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THE IMPACT OF HIGH DENSITY LIPOPROTEIN CHOLESTEROL ON FIVE-YEAR MORTALITY OUTCOMES IN OLDER ADULTS

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The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) guidelines have defined a high density lipoprotein cholesterol (HDL-C) of <50 mg/dL in women and <40 mg/dL in men as a risk factor for cardiovascular disease. Our research aim was to examine the relationship between untreated HDL-C levels below this recommended level on five year cardiovascular, stroke, and all-cause mortality in adults over 71 years of age.

The Established Populations for Epidemiologic Studies of the Elderly (EPESE) is a prospective cohort study of community dwelling adults over 65 years of age in East Boston, MA; Iowa and Washington Counties, IA; New Haven, CT; and Durham, NC. The National Institutes of Aging (NIA) started EPESE to study health, social, psychological, and economic aspects of older adults' lives through extensive annual interviews. The EPESE dataset is further enriched by serum measures including low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol, triglycerides, glucose, BUN and creatinine, which were obtained at the sixth annual follow-up interview.

Our primary outcome was all-cause mortality with secondary mortality outcomes of acute myocardial infarction (AMI), coronary artery disease (CAD) not AMI, and congestive heart failure (CHF). The mean age of our cohort was 78.7 years with the majority being female (63.86%), white (88.15%), and married (52.80%). Just over half (52.07%) of our cohort met the criteria for low HDL-C as defined by ATP III. Chi square and Fisher exact test were used to compare demographics (age, gender, race, marital status, education), clinical variables (history of MI, cancer, diabetes, angina, smoking, alcohol use), and functional variables (activities of daily living, gross mobility, cognitive status) at baseline and five year follow-up. Cox proportional hazard models were created using a step-wise approach to assess the impact of low HDL-C on mortality.

Low HDL-C was not significantly associated with crude all-cause (P= .413), AMI (P= .473), CHF (P= .259), and stroke (P= .345) mortality. HDL-C was significantly associated with unadjusted CAD (P= .033) mortality. However, after adjustment for demographics, clinical, and functional variables as well as the other blood values all outlined above, HDL-C was not associated with five year all-cause, AMI, CAD, CHF or stroke mortality with adjusted hazard ratios of (HR=1.03, 95% CI 0.90-1.18), (HR=1.09, 95% CI 0.70-1.71), (HR=1.33, 95% CI 0.91-1.92), (HR=1.07, 95% CI 0.63-1.81) and (HR=0.80, 95% CI 0.51-1.27) respectively.

In older community dwelling adults enrolled in EPESE, low HDL-C levels as stratified by current recommended guidelines (<50 mg/dL in women and <40 mg/dL in men) were not associated with increased risk of five-year cardiovascular, stroke or all-cause mortality. HDL-C alone may have minimal effect on future longevity in older adults due to competing risk and co-morbid conditions. Further studies are required to determine whether the movement toward more aggressive lipid profile interventions specifically to raise HDL-C in older adults would prove beneficial in this growing segment of our population.

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CHAPTER 1: INTRODUCTION

In the United States, cardiovascular disease (CVD) kills one person every 35 seconds or approximately 2,500 people every day (1). Despite many medical and pharmacological advancements in cardiovascular medicine in the last fifty years, CVD remains our nation's leading killer surpassing the next four leading causes of death (cancer, chronic respiratory disease, accidents, diabetes) combined (1). Older adults aged 65 years and up experience the greatest number of cardiovascular events and 83% of the associated mortality, putting them at particularly high-risk (1-3).

Research continues to assess patients and examine how to best modify known risk factors including high cholesterol, particularly high low density lipoprotein cholesterol (LDL-C), high triglycerides, and low high density lipoproteins (HDL-C) through lifestyle and pharmacological interventions in an effort to curb the morbidity and mortality associated with CVD. The focus of this research is to examine the specific role HDL-C plays as a predictor of mortality in this high-risk segment of the population composed of older adults.

To get a broader sense of HDL-C, we will discuss it in several contexts starting with the molecule itself and its complex role in the

pathophysiology of arteriosclerosis. Next, we will examine the effects of HDL-C on the population level looking at the epidemiological data available. Finally, we will carefully break down the interventional study data and look forward making note of the gaps still in need of more exploration.

The Physiology and Pathophysiology of HDL-C

Our understanding of the role of HDL-C has become more complex in recent years. Long touted as the "good cholesterol", HDL-C has been shown to have both anti-inflammatory and pro-inflammatory effects providing protection in some circumstances and enhancement of arteriosclerosis in others (4,5). Its role in reverse cholesterol transport, in conjunction with the known antioxidant, antithrombotic, and anti-inflammatory properties of HDL-C, all likely contribute to its apparent protective benefits. Likewise, the "paradoxical" negative effects of HDL-C are also related to these same biochemical pathways.

The HDL-C particle pictured in figure 1is composed of a hydrophilic phospholipid outer layer with cholesterol and apolipoproteins enclosing a hydrophobic core of triglycerides and cholesterol esters (6,7). The majority (estimated at 60%-80%) of the apolipoproteins present are apo A-I and are thought to be antiatherogenic (6,8).

Meanwhile about 20% of the apolipoproteins are apo A-II, which have been shown to be proatherogenic in animal models (6,9). The apo A-I containing HDL-C has been shown to play an important role in reverse cholesterol transport, which is summarized in figure 2 (6). Reverse cholesterol transport allows for the removal of cholesterol from the vasculature followed by transport to the gonads and the adrenals for use in sterol production or to the liver and ultimately the bile through which it can be removed from the body (6,9,10). Reverse cholesterol transport specifically allows for the efflux of cholesterol from cell membranes into apo A-I containing lipid-poor pre-β1 HDL-C particles through the binding of apo A-I to the adenosine triphosphate-binding cassette transporter A-1 (ABCA1) in the cell membranes of the vessel walls (6,9). Following its incorporation into HDL-C particles, the cholesterol is esterified by lecithin cholesterol acyl transferase (LCAT) to form large, spherical α HDL-C particles (6). Following esterification, the cholesterol can be delivered to sterogenic tissues (liver, gonads, adrenals) through a family of scavenger receptors (9). Alternately, the particle can be acted upon by cholesterol ester transfer protein (CETP), so that the HDL-C ester is transferred in exchange for triglycerides to VLDL/LDL-C particles, which then make their way to the liver for removal from the body (9). In addition to its direct role in reverse

cholesterol transport, the function of HDL-C as an antioxidant and anti-inflammatory is essential in protecting us from CVD.

Figure 1: High Density Lipoprotein Cholesterol (HDL-C) Particle

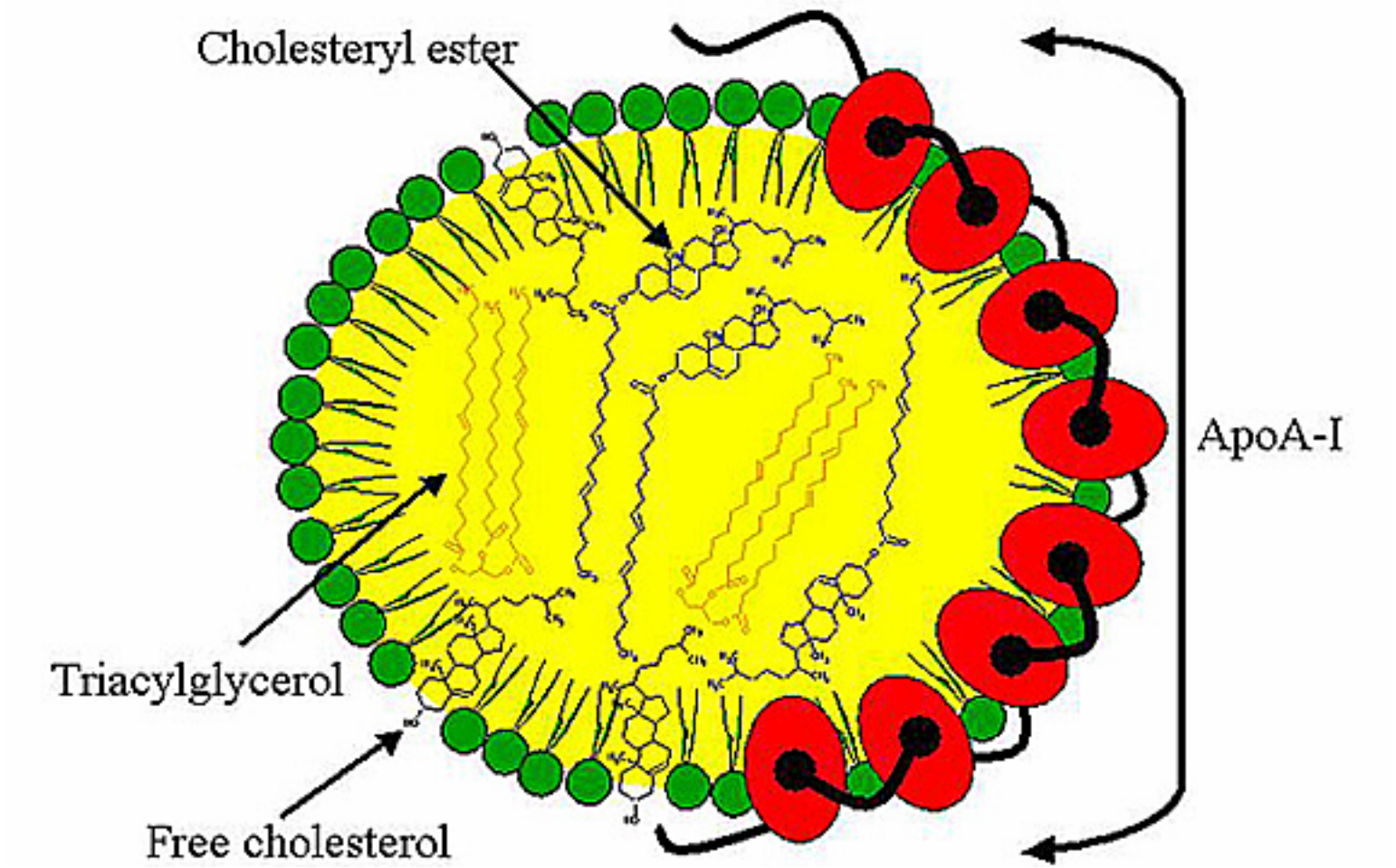
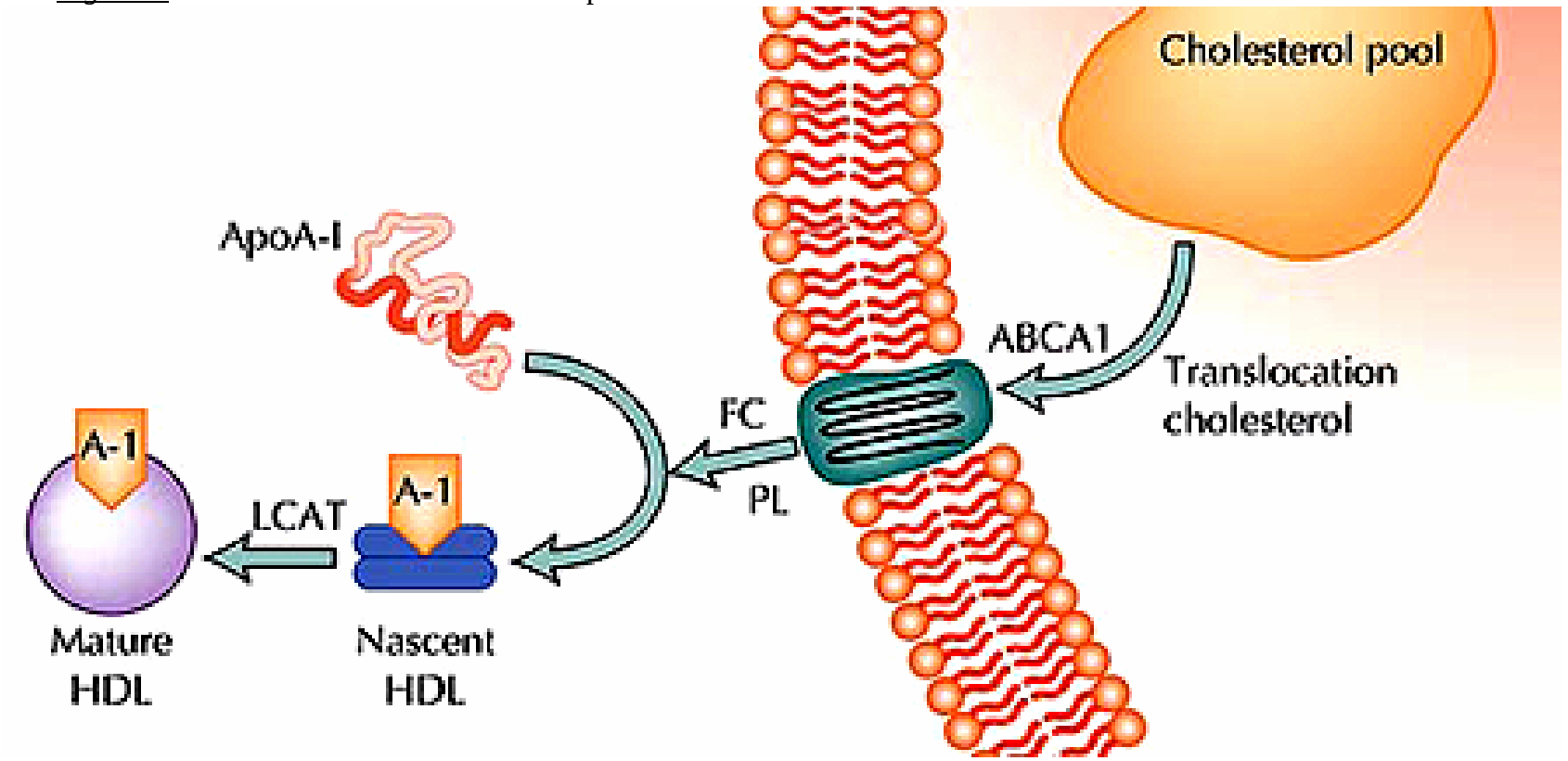


Image taken from <http://www.icb.ufmg.br/pat/imagem/esquema/hdl.jpg> (10)

Figure 2: Reverse Cholesterol Transport



Apolipoprotein A-I interacts with the ABCA-1 receptor to encourage removal of cholesterol from the pool in the cells in the form of free cholesterol (FC) and phospholipids (PL) that can then be picked up by nascent HDL-C. This pre-ß HDL-C is transformed to mature α HDL-C.

Image adapted from <http://www.images.md>

It is widely acknowledged that vascular inflammation plays an important role in arteriosclerosis because endothelial cells within the plaque produce pro-inflammatory cytokines and monocyte chemotaxis protein-1 (MCP-1) (9,11). These cytokines and chemokines attract monocytes and enhance intimal proliferation, leading to further damage of the arterial wall. HDL-C acts as an anti-inflammatory by inhibiting the production of these detrimental cytokines, notably tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) (4,8,12). Secondly, HDL-C acts to regulate the expression of leukocyte endothelial adhesion molecules (vascular cell adhesion molecule-1 or VCAM-1, intracellular cell adhesion molecule-1 or ICAM-1, and E-selectin), thereby protecting the vascular endothelium from invasion by leukocytes and monocytes (4,8,12). It is believed that HDL-C and apo A-I specifically accomplish this by binding and in turn neutralizing lipopolysaccarides and endotoxin; thus, preventing the release of cytokines and also inhibiting the activation of complement (8,9). Since TNF-α and IL-1 are also known to promote coagulation and fibrinolysis, it has been speculated that HDL-C may have an additional protective benefit in inhibiting these processes (9).

HDL-C plays another role in decreasing inflammation as an antioxidant capable of inhibiting phospholipid oxidation of LDL-C and

acting to scavenge other oxidized lipids, like lysophosphatidylcholine (Lyso-PC), that are toxic to the endothelium and smooth muscle cells (4,9,13). LDL-C is oxidized by fatty acid hypoperoxides and is known to contribute directly to vascular inflammation as well as to initiate the formation and propagation of fatty streaks (4,9,13). By protecting the endothelial integrity, HDL-C acts to prevent the progression of arteriosclerosis and helps to maintain the stability of already existing plaques to prevent rupture (8).

However, in the setting of existing CVD, HDL-C can itself become oxidized by a tyrosyl radical (11,14). Oxidized HDL-C has contradictory effects from improving plaque inhibition in mouse models to decreasing reverse cholesterol transport and even encouraging oxidation (11,14). This picture can be further confounded by both acute (infection, as in sepsis or even influenza) and chronic (autoimmune disease, metabolic syndrome) systemic illnesses which are known to lower total HDL-C and encourage its inflammatory properties (4,15-17). The mechanism behind this is thought to involve the binding of HDL-C to ceruloplasmin and serum amyloid A, both acute phase reactants, causing the particle to lose its apo A-I content and become pro-oxidative and pro-inflammatory (9). Paradoxically, the pro-oxidative qualities of HDL-C in individuals with known CVD or

other illness can counteract its protective effects. In age and gender-matched controls, those with CVD possessed a greater portion of pro-inflammatory HDL-C (identified by monocyte chemotaxis assay) despite similar overall levels of total HDL-C leading us to question whether it is the unfavorable ratio of inflammatory to anti-inflammatory rather than overall HDL-C level that is truly to blame (5,18). To parse this apart, we must look beyond the laboratory to population-based studies looking at the effects of HDL-C.

Epidemiological Studies of HDL-C

In the arena of epidemiological research, it has been shown as early as the 1950s that healthy men have higher levels of HDL-C than those with CVD (19). Since then, HDL-C has been shown to be an independent predictor of mortality in the middle-aged population in numerous studies (2,20-22). The landmark epidemiological studies in this area include the Framingham Heart Study, Prospective Cardiovascular Munster (PROCAM) study, and Multiple Risk Factor Intervention Trial (MRFIT) (23-32). Chronologically, we will examine their findings and ultimate impact on how physicians have approached HDL-C as a predictor of CVD in their patients.

The Framingham Heart Study was initiated in the 1940s with 5,209 men and women from Framingham, MA and utilized biannual clinical exams, numerous anthropomorphic measures, blood chemistries, and continual surveillance for morbidity and mortality in an effort to determine the risk factors for CVD; as time went on, this study would ultimately include their offspring as well (1,23,31-33). This groundbreaking study has provided us with the criteria used at the bedside and in the office to determine 10-year cardiovascular risk stratification, including age, blood pressure, smoking status, and lipid profile (1,2,34).

Between 1965-1971, a fasting lipid profile including cholesterol and the lipoproteins was drawn in 2,815 men and women between 49 and 82 years of age and 132 of these individuals would develop new onset CVD within 4 years (35). Those with HDL-C less than 35 mg/dL were 8 times more likely to develop CVD compared to those with HDL-C of 65 mg/dL though application of measuring HDL-C using the methodology of the time could mean a 5 mg/dL error in either direction making risk stratification of those on the borderline difficult (35). The near linear relationship showing decreased risk of CVD with increasing HDL-C was proven through additional studies of this data on its own and pooled with other cohorts (36,37).

Low HDL-C was also shown to be highly correlated to increasing body weight and triglycerides and associated though not statistically significantly with glucose intolerance (35). This clustering of features was likely an early recognition of the combination of features now referred to as metabolic syndrome, which is defined by both the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) and the World Health Organization (WHO) as meeting 3 or more of the following criteria: fasting plasma glucose >110; abdominal obesity with waist-to-hip ratio >0.90 or BMI >30 or waist girth >94 cm; HDL-C <35 mg/dL; triglycerides >150 mg/dL; and blood pressure >130/85 mmHg with the WHO requiring glucose intolerance as one of the three parameters (2,38,39).

Also in an effort to identify cardiovascular risk factors, MRFIT was begun in the 1970s (40). It involved the screening of over 350,000 men between 35 and 57 years of age from 1973-1976 ultimately obtaining a cohort of 12,866 men without evidence of CVD for a longitudinal study (40). The study population was randomized to a special intervention group receiving more intensive treatment for hypertension, dietary

counseling for lipids and smoking cessation counseling, or a second group receiving usual care delivered by their regular non-study physician (41). Studies of both arms of this cohort have shown a statistically significant inverse relationship between CVD mortality and HDL-C level (41). A non-significant trend was also noted for all-cause mortality (41). A meta-analysis done in the 1980s, which included both Framingham and MRFIT, also yielded similar results suggesting that HDL-C has the greatest effect on coronary heart disease (CHD) related events and deaths with little impact on all-cause mortality (42). Yet, this effect is powerful enough that a 1 mg/dL increase in HDL-C results in a 2-3% decrease in yearly CHD mortality (42).

A study published in 2006 on a cohort of MRFIT suggests that metabolic syndrome may also be playing a driving role in the MRFIT HDL-C results in a similar way as with the Framingham data (43). They noted that among men with metabolic syndrome (41.9% of the sample), HDL-C showed a strong predictive relationship with CHD mortality (HR=1.45, CI=1.17–1.54), while it showed a much weaker association among those without metabolic syndrome (HR=1.02, CI=0.86–1.22) (43).

The PROCAM study was begun in Germany in 1979 with initial recruitment through 1985 to examine people for prevalence of cardiovascular risk factors and then longitudinally follow them and track cardiovascular mortality and morbidity with biannual questionnaires, a follow-up exam in 6-7 years and reviews of their death certificates (27,44). Participants were drawn from a self-selected sample of almost 20,000 volunteers aged 16-65 years who worked in 52 different offices or authorities (27,44). Measures included questionnaires, blood pressure readings, anthropomorphic data, electrocardiogram, and blood draws following 12 hours of fasting (27,44).

The PROCAM data showed that although HDL-C level was independent of age, it remained 12 mg/dL lower in men compared to women (44). Further analysis of cardiovascular events was confined to men over 40 years of age because other groups lacked an adequate number of events for study over the 6-year follow-up period (44). This cohort of 4,559 men aged 40-65 years, was broken into those with CHD (fatal and non-fatal MI or other sudden cardiac deaths) and those without CHD (4,221 men, living with no confirmed events) (44). There was a statistically significant difference ($P<.0001$) in the mean HDL-C between the CHD (39.5 mg/dL) and non-CHD (45.2 mg/dL) groups

with a greater percentage of those with lowest HDL-C <35mg/dL present in the CHD group (45.2% versus 16.2% in non-CHD) (44). Those with HDL-C <35 mg/dL also made up the greatest portion of the CHD group (44). This PROCAM study data has shown a four-fold increased risk of CHD in those with an HDL-C of <35 mg/dL (44).

These three studies have provided invaluable information with regard to systematically defining cardiovascular risk factors and determining how to translate them into a schema of risk stratification with which a physician can readily identify high-risk patients before they suffer morbidity or mortality associated with CHD. Likewise, all have shown that HDL-C is an independent risk factor inversely related to CHD mortality, particularly at levels below 35 mg/dL. Yet they have provided us with data primarily looking at middle-aged adults comprising those in their 40s-60s (2,20-22,42,44). Those over 65 years of age experience the greatest number of cardiovascular events and deaths each year, so it is important to examine some of the literature devoted explicitly to this uniquely at-risk population (1-3).

One such study is The Established Populations for Epidemiologic Studies of the Elderly (EPESE), which is a prospective cohort of community-dwelling adults over 65 years of age in East Boston, MA;

Iowa and Washington Counties, IA; New Haven, CT; and Durham, NC (45). The National Institutes of Aging started EPESE to study health, social, psychological, and economic aspects of lives of older adults with extensive longitudinal follow-up along with morbidity and mortality surveillance (45). Much of the research on this cohort has focused on the cognitive and physical functional data, as well as depressive symptoms and social interactions to determine what best predicts successful aging (46-51).

The EPESE dataset is further enriched by serum measures including low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol, triglycerides, glucose, BUN and creatinine along with numerous other parameters, which were obtained at the sixth annual follow-up interview (52). This group is commonly referred to as the MacArthur cohort and has provided a well-defined group of people on which there is a wide breadth of lifestyle and health measures in addition to the serum values allowing research to place these quantitative measures in a unique context.

Previous studies of EPESE population that have examined the predictive value of cholesterol and HDL-C yielded conflicting results (52,53). The first found that serum cholesterol levels were not

predictive for cardiovascular disease (defined as coronary heart disease or acute myocardial infarction) or all-cause mortality in the very elderly (>80 years of age) (52). Low HDL-C was associated with an increased risk of CHD, but these findings were not significant (52).

Another study examined the predictive value of serum cholesterol and HDL-C for CHD mortality excluding individuals with a prior history of cardiovascular disease (52,53). Low HDL-C (defined as <35 mg/dL) was shown to significantly increase risk of CHD in those 70-80 years of age with a similar trend of borderline significance in those >80 years of age (52,53). Even HDL-C in the normal range (35-59 mg/dL) was associated with increased risk of death from CHD (52,53).

These findings are in agreement with much of the data present in the middle-aged population suggesting the inverse relationship between HDL-C and cardiovascular mortality risk. Likewise, the presence of this trend in those with normal HDL-C levels falls in line with the concept that an increased percentage of pro-inflammatory HDL-C may be present in those with CVD even if their total levels are relatively normal. It also reinforces the finding that total cholesterol is not an independent risk factor in this age group. Yet, there is no other current study looking at specific cardiovascular mortality outcomes in

the entire cohort with adjustment for functional health. This adjustment could theoretically serve as a proxy for general wellness; thus, providing new insight into the role HDL-C plays in this statin naïve population (54).

Interventional Studies of HDL-C

The first series of interventional studies looking at HDL-C took into account lifestyle interventions including exercise, smoking cessation, and weight loss (55). As we have learned more about the physiology behind HDL-C and what it means at the population level, the whole cholesterol and lipoprotein landscape has been reshaped by lipid-lowering medications.

First, we will look at the effects of lifestyle modification on HDL-C level and CVD. Next, we will examine the classes of lipid-lowering medications most notably HMG-CoA reductase inhibitors (statins), fibrates, and nicotinic acid looking specifically at their effects on HDL-C. Other lipid-lowering medications that are used, but have little to no effect on HDL-C, include bile sequestrants, cholesterol absorption inhibitors, and neomycin; thus, these will not be reviewed here.

Lifestyle interventions including smoking cessation, diet and exercise, and weight loss all affect HDL-C levels (55). It has been shown that ≥20 cigarettes a day causes a dose-dependent reduction in HDL-C from 11-14% (55-57). Body mass index (BMI) is also inversely related to HDL-C levels with lower levels found among those with higher BMIs (58). Regular exercise has been associated with higher HDL-C levels as well, but the greatest gains in HDL-C are shown in sedentary overweight individuals who engage in high levels of high intensity exercise rather than low levels of more moderate exercises (59,60). Of note, during active weight loss HDL-C levels appear to go down, but once weight stabilizes the HDL-C levels too appear to stabilize in accordance with the new weight allowing for an increase of 2 mg/dL for each 4.5 kg lost (61).

In addition to lifestyle changes, lipid-lowering medications and other medications can also influence HDL-C levels (57). Nicotinic acid, a niacin derivative, provides the greatest increase in HDL-C of 15-35% (57). Nicotinic acid discourages the production of very low density liporoteins (VLDL) and thereby lowers triglyceride levels (57). However, its effects on HDL-C are thought to be related to encouraging reverse cholesterol transport because nicotinic acid inhibits the removal of apo A-I from HDL-C particles without decreasing the removal of cholesteryl

esters by hepatocytes in vitro (57). The major side effect is flushing and can be controlled with time-release preparations and pre-treatment with a prostaglandin inhibitor such as aspirin (57). Unfortunately, nicotinic acid can increase glucose intolerance and thereby diabetics must be carefully monitored (57). Also, in doses above 3 g per day there is an increased risks of liver function test abnormalities (57). Currently, niacin is often used in conjunction with another lipid-lowering medication, notably statins, to good effect as shown by the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study where extended release niacin was added to already existing statin regimens (62).

Fibrates (gemfibrozil, fenofibrate) increase lipoprotein lipase activity and decrease triglycerides (57). With the increased catabolism of triglyceride heavy particles, more raw materials are available for HDL-C production allowing for a moderate 10-15% increase in levels (57). Fibrates are used fairly regularly and have also been used in conjunction with the statins for better lipid control.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors), or statins, are the standard for lowering LDL-C, yet they have a only modest effect on increasing HDL-C of 5-10% (57).

The mechanism of inhibiting HMG-CoA reductase leads to a reduction in LDL-C receptors enhancing clearance of apo B containing lipoproteins (pro-inflammatory), thus preventing the transfer of cholesterol from them to apo A containing lipoproteins (57). Though they have little effect on total HDL-C levels, statins have been shown to increase the ratio of anti-inflammatory to pro-inflammatory HDL-C by this mechanism (11). Statins allow for the greatest impact on HDL-C in the setting of a very low level with a concurrently very elevated triglyceride level (57). However, in those with existing CVD, the change in the ratio of anti-inflammatory to pro-inflammatory HDL-C does not return to that of unaffected individuals (11). Ultimately, the benefit of statin therapy for improved outcomes in CVD is evident, but it cannot be directly linked to this change in HDL-C function because there is also a concurrent change in LDL-C (63,64).

In addition to those specifically designed to treat lipid disorders, there are other drugs that also affect HDL-C levels including α-blockers, estrogens, and alcohol (57). Similarly to fibrates, α-blockers are thought to increase lipoprotein lipase activity to create an increase in overall HDL-C production (57). Estrogen in the form of oral contraceptives has also been shown to raise HDL-C levels 10-15% by increasing apo A-I production and encouraging lipase activity in

hepatocytes (57). Yet, estrogen can also significantly increase triglycerides known to often be elevated anyway in the setting of low HDL-C, so these drugs must be monitored carefully in these patients (57). Moderate ethanol intake has been shown to also raise HDL-C, but this effect is lost when consumption increases to levels seen in alcoholics and the positive effects are lost with cessation of alcohol consumption (57).

Finally, we will review three of the major interventional trials that have examined the effects of various pharmacological interventions on HDL-C level, namely the Veterans Affairs High-density Lipoprotein Intervention Trial (VA-HIT), the Bezafibrate Infarction Prevention (BIP) trial, and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).

VA-HIT is a trial designed to explicitly look at how treatment with gemfibrozil affects HDL-C levels with a primary outcome of nonfatal or fatal MI or other CVD related death (65). A cohort of 2,531 men ≤74 years of age with CHD, an HDL-C level of ≤40 mg/dL, and an LDL-C ≤140 mg/dL was recruited from 20 Veterans Administration medical centers across the country (65). The study population was notable for advanced age of 64 years, very low HDL-C with a mean of 32 mg/dL,

and a high prevalence of both diabetes (25%) and hypertension (57%) (65). The half of the cohort receiving 1200 mg gemfibrozil daily had an HDL-C increase of 6%, total cholesterol decrease of 4%, and triglyceride decrease of 31% with no significant change in LDL-C levels compared to the placebo control group following one year of treatment (65,66). This cohort showed that treatment of high-risk individuals with very low HDL-C and moderately elevated LDL-C can benefit from intervention showing a significant reduction of 22% in both CHD related death and nonfatal MI at 5-year follow-up (65). The VA-HIT is also unique because the effect of increasing HDL-C is not confounded by a concurrent decrease in LDL-C, which has independently been shown to decrease cardiovascular risk (66). This interdependence of LDL-C, triglycerides and HDL-C in predicting primary CVD morbidity and mortality with gemfibrozil was also demonstrated by the Helsinki Heart Study (67). In addition, VA-HIT included a cost-benefit analysis showing that treatment with relatively inexpensive gemfibrozil would actually be cost effective in decreasing future health expenditures in this population (65).

Similar to VA-HIT and its analysis with regard to primary prevention, the BIP study examines the effect of another fibrate, bezafibrate, on secondary prevention of CVD morbidity and mortality (67). At initiation

in 1990, the aim of BIP was to look at whether increasing HDL-C and decreasing triglycerides using bezafibrate would affect nonfatal MI rates and CVD mortality in those who have already had a nonfatal MI or established CAD, HDL-C level ≤45 mg/dL, and modestly elevated total cholesterol (67). Between the bezafibrate and placebo arms, there were 3,122 men and women between the ages of 45 and 74 who participated with just over 60% having a previous MI and approximately 30% with a history of unstable angina (67). Those in the bezafibrate group experienced an 18% increase in HDL-C and a 21% reduction of triglycerides (67). Despite these dramatic effects, bezafibrate did not demonstrate a significant difference when compared with placebo group in repeat nonfatal MI or CVD-related death over the mean 6.2 year follow-up period of this study nor in later studies looking at 7.9 year mean follow-up (67,68). It is believed that the addition of open-label lipid-lowering therapy in both the placebo (15%) and intervention groups (11%) may have been a confounding factor (67-69). Of note, the mortality benefit of bezafibrate's effect on HDL-C was only evident in post hoc analysis of those with triglycerides ≥200 mg/dL at baseline suggesting that triglycerides may be the force driving the apparent benefit of HDL-C in other studies (67). The differences between BIP and VA-HIT have been attributed to the clear differences between the study population with the VA-HIT population

being older with more co-morbidities, and more deranged lipid profiles compared to the BIP cohort (67-69).

AFCAPS/TexCAPS placed special emphasis on examining the impact of HDL-C and other lipid molecules on CVD since this cohort had what was considered an average total cholesterol (180-264 mg/dL) and LDL-C levels (130-190 mg/dL) prior to the revised guidelines recommending lower levels in 2001 (2,70). HDL-C levels for inclusion were ≤45 mg/dL for men and ≤47 mg/dL for women with triglycerides <400 mg/dL (70). This cohort of 6,605 men 45-73 years of age and postmenopausal women 55-73 years of age was treated with 20-40mg of lovastatin, an HMG-CoA reductase inhibitor, daily versus placebo (70). This intervention decreased the risk of acute major coronary events (AMCE) including fatal and nonfatal MI, unstable angina and sudden cardiac death with incremental changes in risk of 11% for each 5mg/dL change of HDL-C from baseline to one year follow-up (70). Yet this could also represent the effects of the broad benefit of statins lowering the total cholesterol and LDL-C level, as well as increasing HDL-C. However, within the mortality model LDL-C was not predictive of AMCEs following treatment and the more useful measures were lipoprotein components of HDL-C, namely apo B which was significant both at baseline and follow-up and apo A-I as a component of apo

B/A-I (70). So, in those at moderate risk for new events, apo B and apo A-I may be more useful measures to assess the effectiveness of treatment with a statin.

Gaps in Knowledge

There is a lack of both epidemiological and interventional data for HDL-C in older adults >65 years of age, especially when taking into account the more strict recommended guidelines for lipid treatment introduced in 2001 (70). Yet there is also a gap when it comes to understanding the unique circumstances and qualities of older adults and their impact on lipid levels as well. For example, functional status can have an overarching affect on other areas of an older person's life. Higher functioning individuals who are more likely to be community dwelling and more mobile typically have higher HDL-C levels, which are negatively correlated with visceral adiposity (suggestive of metabolic syndrome) compared to their non-community dwelling age-matched counterparts who have lower HDL-C levels showing no relationship to their waist girth (71,72). Therefore, individuals capable of living independently tend to be in better general health with potentially better though not necessarily "ideal" lipid profiles as compared to their institutionalized counterparts who are more likely to be affected by chronic illness.

Similarly, those older individuals with multiple co-morbidities are more likely to be home bound or in a long-term care facility. On a pathophysiological level, both acute and chronic systemic illness and inflammation, which are more often present in this population, can also play an important role in the progression of cardiovascular disease placing HDL-C in a setting where it may behave paradoxically to feed into this cycle rather than protect (4,11,14-17).

It has also been shown that these same functional outcomes are important to determining which elderly patients may be at greatest risk for death over the next year since many experience a steeper decline in function prior to death (49-51). With this in mind, it is important to consider a different schema when setting lipid treatment goals in an older population where the focus may be less on a particular number and lengthened lifespan, but on the quality of those years gained without loss of functioning (47).

CHAPTER 2: STATEMENT OF PURPOSE

According to the 2000 United States Census, there are 26.5 million people over 70 years of age who make up about 9% of our country's total population with the fastest growing segment being the oldest-old who are 85 years of age and up (73). The population of older adults will only continue to grow as the first of the "baby boomers" turn 60 years old in 2006 (74). This group of 75 million individuals born in the post-World War II period from 1946-1964 represented 28% of the population in 2000 with the majority born between 1946-1950 (74). It is clear that our society will face many new clinical and economic healthcare challenges as our population ages in the coming decades. For this reason, we will be forced to more closely examine and plan for the treatment and management of older adults especially with regard to the chronic complications of cardiovascular disease, which remains the leading cause of morbidity and mortality in our population.

Many large-scale epidemiological studies defining over 200 risk factors governing cardiovascular disease have shaped both how we see our patients and how we view our role as a physician. Now there is a new focus towards aggressive treatment and active prevention of cardiovascular disease and its life altering and life ending consequences (75-77). Recommendations like the ATP III guidelines

serve to provide physicians with a benchmark consistent with current data in order to best manage their patients to achieve a reduction morbidity and mortality.

HDL-C is an important independent clinical risk factor for cardiovascular disease in the middle-aged population as proven by epidemiologic data from large studies including the Framingham Heart Study, MRFIT, PROCAM, and others (2,20-22). Despite this, data regarding the clinical utility of using HDL-C levels in the older adults (65 years of age) are scant and conflicting (52,53,78-82). Statistical adjustments for cardiovascular risk factors and the common co-morbidities including hypertension, angina, previous myocardial infarction, diabetes, cancer and smoking history have lead to conflicting results in cardiovascular disease mortality in this population.

Similarly, the widespread use of lipid-lowering medications can also be a confounding factor for multiple reasons. As we have seen, several including niacin and fibrates can have significant effects directly on HDL-C levels (57,83). Many are also prescribed in the form of combination regimens, which can influence all plasma lipids and cause confounding effects with regard to lowering LDL-C levels (63,64).

LDL-C is acknowledged to be a strong predictor of cardiovascular morbidity and mortality independently, so it presents a difficulty in determining where the benefit is gained (2). Finally, there is also the question of whether the statins provide additional anti-inflammatory benefits that may indirectly affect HDL-C levels (11).

The EPESE data set provides a unique opportunity to determine the long-term prognostic importance of HDL-C in older adults. As a large data set, which enrolled adults over the age of 71 years who were followed for over 10 years, EPESE provides a prospective cohort with detailed demographic, clinical, laboratory, and functional status data with which this important question can be answered. This population was also mostly naïve to lipid-lowering therapies with only 1% being exposed to these types of medications allowing us to examine how untreated HDL-C levels influence mortality; thus, avoiding some of the confounding effects of the medications (54). This aspect is of special importance as we look towards a future of more aggressive lipid management regimens with tighter therapeutic targets.

Looking to current ATP III guidelines, it is important to examine what these cutoffs mean in terms of mortality for older adults with specific attention on HDL-C. We have stratified our population in accordance

with these guidelines for HDL-C of <50 mg/dL in women and <40 mg/dL in men (2). Our research aim was to examine the relationship between untreated HDL-C levels below this recommended level on five year mortality in adults over 71 years of age. Our primary outcome was all-cause mortality with secondary mortality outcomes of acute myocardial infarction (AMI), coronary artery disease (CAD) not AMI, and congestive heart failure (CHF). The serum measures including LDL-C, HDL-C, total cholesterol, triglycerides, glucose, BUN and creatinine along with demographics and clinical and functional variables provide information for appropriate statistical adjustment to account for both cardiovascular and other risk factors influencing mortality (52). With these methods, we aim to isolate as much as possible the effect of stratifying patients along current HDL-C goals in an effort to examine if these are reasonable guidelines for an older population.

CHAPTER 3: METHODS

Study Sample & Data Collection

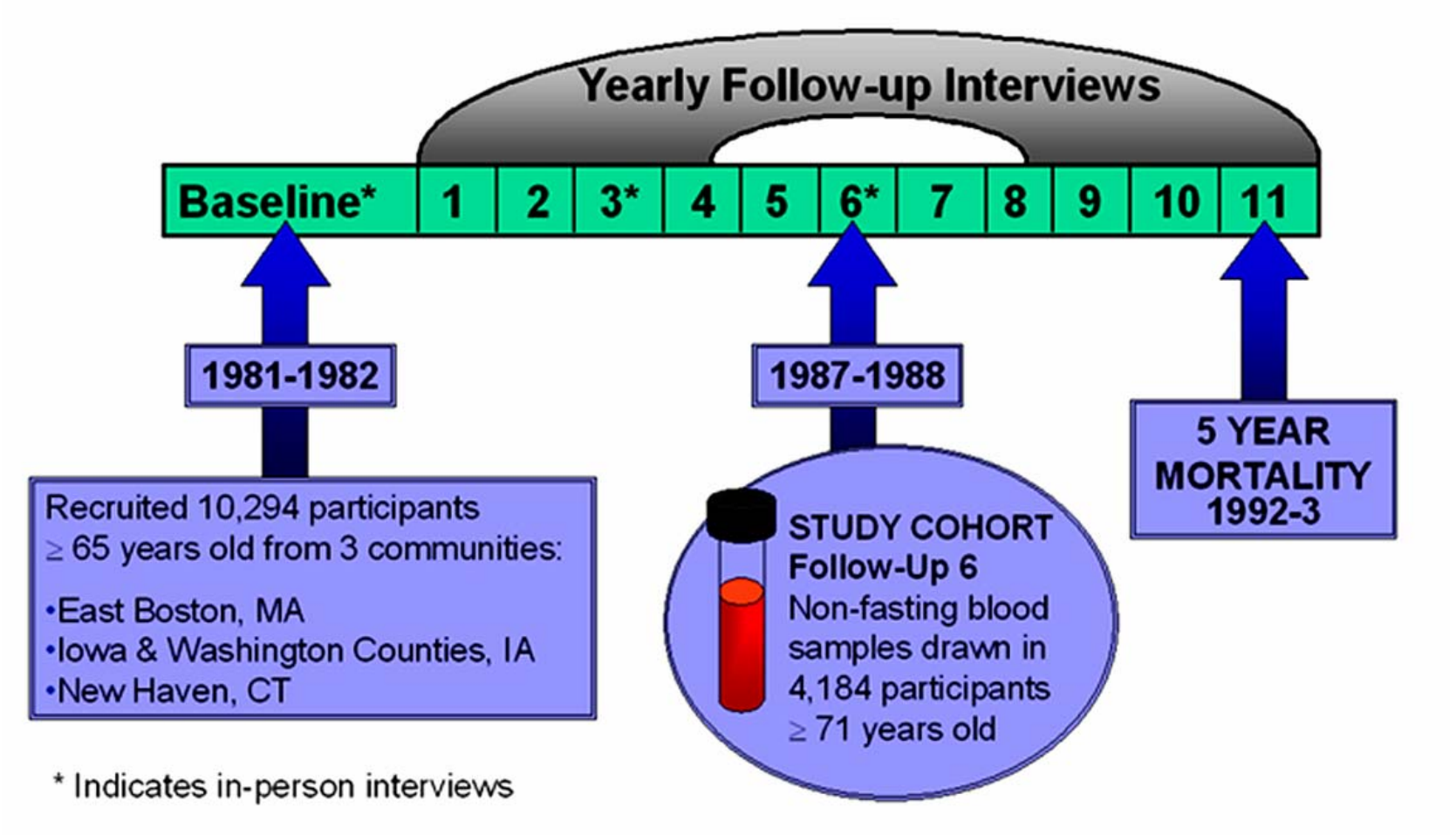
The Established Populations for Epidemiologic Studies of the Elderly (EPESE) was initiated in 1980 by the Epidemiology, Demography, and Biometry Program (EDBP) at the National Institutes of Aging to study health, social, psychological, and economic aspects of older adults (45). EPESE incorporates cross-sectional data and continued annual surveillance of 14,456 older persons age 65 years and above (45). The timeline of study events is described as follows with a visual summary presented in Figure 3.

Study participants were recruited from 3 communities: East Boston, MA (n=3809), Iowa and Washington Counties, Iowa (n=3673); and New Haven, CT (n=2812) between 1981 and 1982 with an additional 4th site in North Carolina (n=4162) added in 1986 (45). In East Boston and the Iowa counties, the study participants were a representative sample of the total population ≥65 years of age (45); In New Haven, the participants were derived from a random sample of residents stratified by housing type and sex (45,52). Between 80 and 84% of eligible persons in the three communities participated (45).

Participants were followed from 1981 to 1988 with annual in-person and telephone interviews. During the in-person interviews (which were done at baseline and at the 3rd and 6th follow-up points), participants were asked about their health habits, functional status, chronic conditions, and hospitalization history and had their blood pressure measured at home (45,52).

In 1987-88, blood samples were obtained from about 41% of the original participants ≥71 years of age providing 5,940 useful measures of various serum values and markers including total cholesterol, HDL-C, triglycerides, glucose, BUN, and creatinine along with numerous others (52).

Figure 3: Established Populations for Epidemiologic Studies of the Elderly (EPESE) Timeline



Demographic Variables

The demographic variables in this study included age, sex, race, marital status, and education. The author examined the questions available in the entire EPESE dataset for all sites and time points. The answers for these demographic questions were then recoded as categorical variables for use in the statistical model. Age was calculated from date of birth reported by patient at baseline. Race was classed as white and non-white based upon participants' self-report. Marital status was classed as married and not married (separated, divorced, and widowed combined) and changes in status were updated yearly. Education level was classed as < 7 years (yes/no), which was chosen to correspond with the completion of elementary school. The original text of these questions is included in Appendix 1. These baseline characteristics are summarized in Table 1.

Table 1: Baseline Demographics of the Study Cohort

Baseline Demographics	**East Boston**	**Iowa**	**New Haven**	**Totals**
Number	1248	1939	997	4184
Sex, % Female	64.02%	64.98%	61.48%	63.86%
Race, % White	N/A	94.64%	75.53%	88.15%
Mean Age, years	77.91	79.07	79.03	78.67
Marital Status, % Married	52.40%	59.62%	40.02%	52.80%
Mean Education, years	9.11	10.76	9.47	9.78

All eligible participants were ≥71 years of age at the time of the blood draw. Persons eligible who declined the blood draw tended to be older, had more disability, were more likely to be hospitalized in the last year, but no differences between groups were noted for sex, education, smoking history, or recent diagnosis of cancer (53).

Clinical Variables

Clinical variables were obtained in conjunction with the EPESE study at set time points. Seated blood pressure data was obtained three times taken at each in-person interview (baseline, follow-ups 3 and 6) in accordance with the Hypertension Detection and Follow-up Program protocol and calculated by taking the mean of second and third readings (52,84). We calculated pulse pressure by finding the difference between the mean systolic and mean diastolic blood pressure. Likewise, we calculated body mass index (BMI) using the participant's weight in kilograms divided by the square of height in meters.

The author used previous studies of CVD to create a pertinent list of clinically relevant covariates. Many including cancer, diabetes, hypertension, and myocardial infarction were present in the EPESE

dataset as simple yes/no medical history questions with built in examples of lay explanations. Previous studies utilizing EPESE and the EPESE dataset itself were used to determine the appropriate question to elicit the symptoms of unstable angina (52). Medical history of cancer, diabetes, hypertension, angina, and myocardial infarction were self-reported (yes/no) at baseline and follow-up. The baseline characteristics are summarized in Table 2. The text of these inquiries is also included in Appendix 1. The author added yearly new onsets of these symptoms or conditions over the five-year time period to the baseline to obtain complete numbers at 5 years.

History of lipid disorders was not taken. Lipid-lowering medication use was self-reported and found to be about 1% in previous studies affecting 46 of the 4128 participants (54), so this variable was not included in our analysis.

Health related lifestyle covariates included alcohol (wine, beer, hard liquor) use in the previous month and smoking history obtained at baseline. The author combined alcohol use of any type and classed it as a categorical variable (yes/no). Past and present smokers were included in the variable for those with a history of smoking and this information was also recoded categorically (yes/no).

Table 2: Baseline Clinical Variables in Study Cohort

Baseline Clinical Variables n (%) except where noted	**East Boston**	**Iowa**	**New Haven**	**Totals**
Drank Alcohol (wine, beer, liquor) in last month	753 (60.34%)	578 (29.81%)	529 (53.06%)	1860 (44.46%)
History of Smoking	542 (43.43%)	516 (26.61%)	459 (46.04%)	1517 (37.98%)
BMI, mean	27.36 (± 4.72)	26.24 (± 12.50)	26.74 (± 17.87)	27.74
Blood Pressure, Systolic >160	128 (10.26%)	214 (11.04%)	114 (11.43%)	456 (10.90%)
Blood Pressure, Diastolic <90	1165 (93.35%)	1719 (88.86%)	863 (86.56%)	3747 (89.96%)
Antihypertensive Treatment	413 (33.09%)	621 (32.03%)	323 (32.40%)	1357 (32.43%)
History of Diabetes	168 (13.46%)	145 (7.48%)	112 (11.23%)	425 (12.64%)
History of Cancer	195 (15.63%)	245 (12.64%)	137 (13.74%)	577 (16.47%)
History of MI	110 (8.81%)	192 (9.90%)	103 (10.33%)	405 (11.54%)
Exertional Chest Pain	37 (2.96%)	41 (2.11%)	34 (3.41%)	112 (2.68%)

Functional Variables

Through the examination of the EPESE dataset of questions related to function, the author put together a representative set of validated instruments containing questions asked consistently through all study sites and available at both the baseline and 6th follow up time points. The functional covariates that were included were obtained through these instruments and assessed various levels of physical and cognitive functioning.

Performance of activities of daily living (ADLs) was assessed by counting each task (bathing, dressing, toileting, transferring, and feeding) the participant had difficulty doing (85). An ADL score of 0 suggests no difficulty with any of these tasks, while a score of 5 indicates problems with all of them.

Gross mobility was determined by asking if the participant was able to do heavy work around the house, walk a flight of stairs and walk a half a mile (86). Each difficulty was scored as 1 just as with ADLs on a scale of 0-3.

More complex physical performance was determined by noting difficulties with pushing or pulling a large object across the floor, stooping down, writing, and reaching for objects (87). This was scored similarly with a scale of 0-4.

Cognitive function was assessed with the nine question version of the short portable mental status questionnaire (SPMSQ), which assesses the participant's orientation, memory, attention, and fund of knowledge (88). Errors on the SPMSQ were recorded on a scale of 0-9.

The baseline and follow-up mean scores on all these instruments are recorded in Table 3. The specific text of the questions sorted by instrument is included in Appendix 1.

Table 3: Baseline and Follow-up 6 Functional Scores on

Functional Variables	EAST BOSTON		IOWA		NEW HAVEN		TOTALS	
	Baseline	Follow-up 6	Baseline	Follow-up 6	Baseline	Follow-up 6	Baseline	Follow-up 6
ADL Difficulties 0-5, mean	0.003	0.002	0.004	0.017	0.009	0.037	0.010	0.019
Gross Mobility 0-3, mean	2.42	2.05	2.52	2.18	2.33	1.81	2.34	2.02
Physical Performance Difficulties 0-4, mean	0.45	0.50	0.30	0.60	0.42	0.44	0.44	0.51
Cognitive Status (SPMSQ) 0-9, mean errors	1.24	1.57	0.66	1.12	1.30	1.58	1.03	1.42

Blood Values

Blood samples were obtained at participants' homes in the morning following the interview and processed within 8 hours of collection (52,89). These values are listed in full in Appendix 2. Participants were non-fasting at the time of the blood draw, but fasting serum cholesterol and HDL-C values have been shown to correlate with post-prandial values in both normal controls (non-elevated at baseline) and those with baseline hypercholesterolemia (90,91). Triglycerides and glucose measures are less reliable when taken in the non-fasting state.

The cut-offs for blood values were chosen in accordance with the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) recommendations (2). The blood cut-offs (yes/no) for: depressed HDL-C <40 mg/dL for men and <50 mg/dL for women, ideal triglycerides <150 mg/dL, LDL <200 mg/dL (very elevated), impaired renal function BUN >40 mg/dL or creatinine >2 mg/dL, and impaired glucose tolerance glucose >110.

Outcome Variables

Five-year all-cause mortality from the time of the blood draw is considered the primary endpoint. Secondary endpoints include breakdown of the all-cause mortality into the categories of cardiovascular and stroke mortality. Deaths classified as acute myocardial infarction (AMI), coronary artery disease (CAD) not AMI, and congestive heart failure (CHF) were considered cardiovascular in nature. Death certificates are obtained at all centers and the cause of death is reviewed and coded by a certified nosologist using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (52,92). The inherent limitation of death certificate miscoding for cardiovascular causes of death, which is thought to approach 24% is an unavoidable limitation of this study (93,94).

Statistical Analysis

Most variables were classified categorically as outlined above. For functional scales, the categorical responses (yes/no or correct/incorrect) were summed to create a composite score. During the study period, the new onset of chronic conditions was accounted for by summing these new onsets annually and adding them to the baseline.

Chi-square and Fisher exact test were used to compare demographic, clinical, and functional variables at baseline and 5 years later. Univariate analysis of demographics, clinical variables, functional variables, and serum measures with cause of death was performed for both these time points. Our group's statistician programmed this analysis of the variables as defined by the author.

A series of Cox proportional hazards models were developed in a step-wise fashion to assess the association between low HDL-C cholesterol (< 40 mg/dL in men and < 50 mg/dL in women) with five-year cardiovascular and all-cause mortality as outcomes. Ties were handled using the Breslow approximation (95). The potential confounders included in the adjusted model were those demographic, clinical and functional variables outlined above. A best-fit modeling approach was also used to examine the impact of different independent variables on the model as shown in Appendix 3. The programming of the model was written and executed by our group's statistician and the modeling data was then used to determine the pertinent covariates necessary for a statistically sound, yet parsimonious final model. All analyses were performed using SAS version 8.02 statistical software (SAS Institute, Inc., Cary, NC) and included in Appendix 4.

Limitations

One limitation of this study is that it is observational and the data are now 12 years old and do not incorporate newer therapies now being used for hypertension, lipid and glucose control. Even with the introduction of these new therapies, it is unlikely that the risk for such conditions has substantially decreased over time. Since blood samples were obtained from 65% of participants, there are some differences noted between those who gave blood and those who did not. Persons who refused were older, had more disability, and were more likely to have been hospitalized in the previous year, but no differences between groups were noted for sex, years of education, current smoking status, or recent diagnosis of cancer requiring hospitalization (53). Biochemical variables of interest (cholesterol, HDL-C, triglycerides) were obtained only once and within-individual variability could not be considered nor could changes be observed over time.

Despite these limitations, EPESE is the most extensive existing database of older patients that prospectively obtained both biochemical data and functional data with extensive long-term follow-up. The large population and the detail of clinical data already collected provides a basis for efficient statistical analysis to determine the value of HDL-C as

a predictor of clinical outcomes of an elderly population, which is often neglected in the arena of randomized clinical trials.

Ethical Considerations

Since data collection has been completed and EPESE is a closed data set, participant confidentiality was the greatest ethical concern in this research study. All data examined by this study has already been coded by the main EPESE research center such that each individual has received their own number and is only identifiable by that number and by particular site area. Data meets HIPAA de-identification criteria. The data collection for the EPESE project has been closed at all sites in 1991-2, but the mortality continued to be recorded and coded past that time by the EPESE research center.

This study was approved by the Yale University School of Medicine Human Investigations Committee (Appendix 5, HIC Exemption from Review).

CHAPTER 4: RESULTS

Study Sample

Total initial enrollment in EPESE included 14, 456 people over 65 years; therefore, the eligible participants were ≥71 years of age at the time of the blood draw, which occurred at the 6th annual follow-up. Approximately 41% of this group agreed to provide blood samples. Those without a serum sample were excluded from analysis (n=8516). Since North Carolina 5-year mortality data was incomplete, these samples (n=1756) were also removed from analysis. Likewise, those without complete serum measures of interest (total cholesterol, HDL-C, triglycerides, glucose, BUN, and creatinine) were also excluded (n=70). These exclusions are not mutually exclusive and are summarized in Table 4.

Table 4:

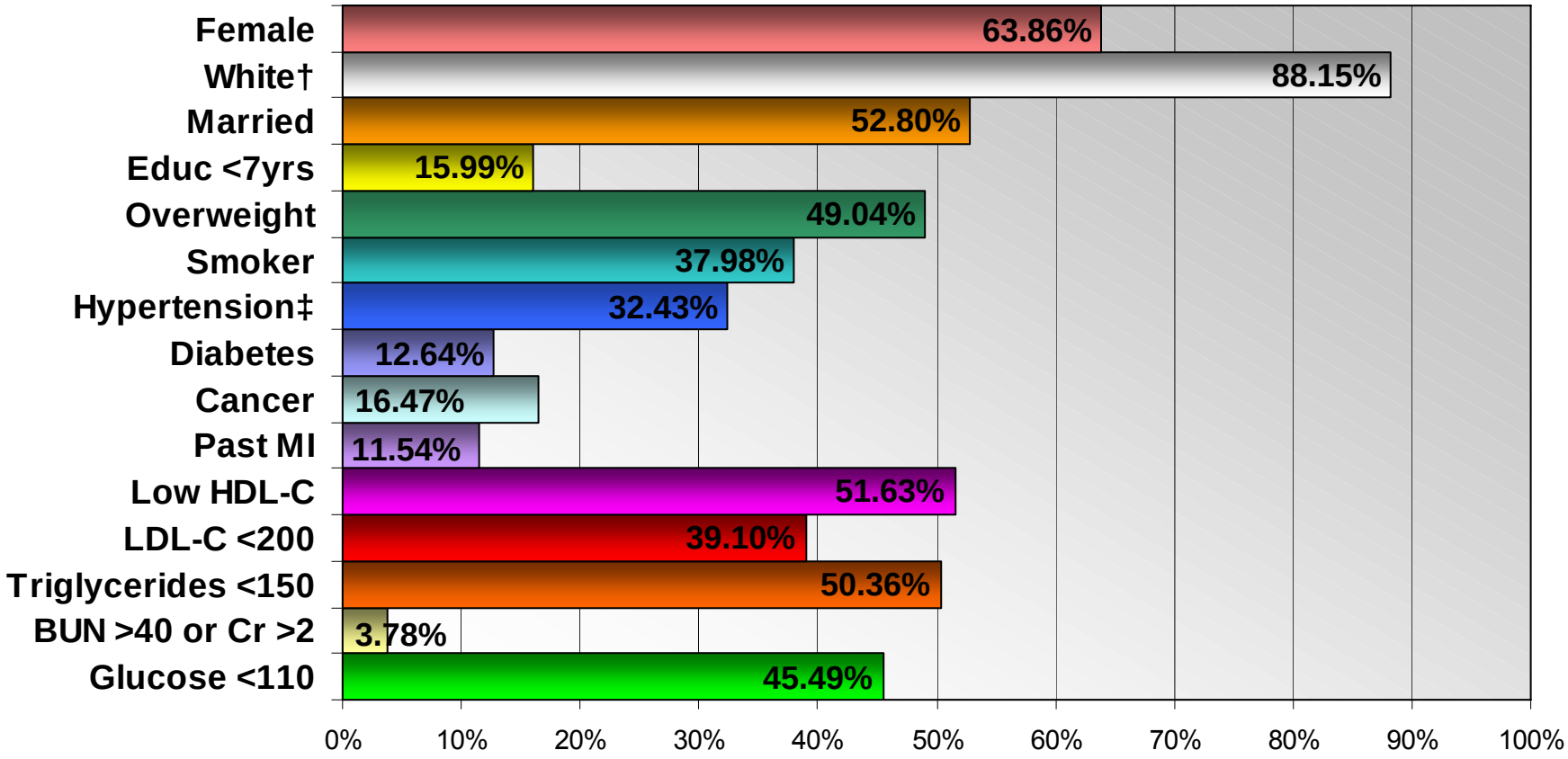
Total Sample	**Number of Participants**
Total EPESE participants (4 sites)	14, 456
EPESE participants w/ serum samples available	5,940
Exclusions:	
NC site complete 5 yr mortality from blood draw not available for final model	1,756
Participants w/ incomplete serum measurements	70
Total Exclusions*	1,812
Final study sample (3 sites)	4,128

* Exclusions are not mutually exclusive

Each individual site cohort and total study cohort examined here are comparable in demographic and lifestyle characteristics, cardiovascular risk factors and prevalence of cardiovascular disease to the whole EPESE study population and respective site populations. However, the North Carolina cohort (not included) with serum samples is primarily non-white and has a greater percentage of individuals with <7 years of formal education compared to the East Boston, Iowa, and New Haven cohorts used in this study.

Overall, the majority of participants included in the final study sample were female (63.9%) and of white race (88.2%, excluding East Boston where race data was not collected). The mean age of these participants was 78.7 years of age, ranging from 70 to 103 years of age across the three sites. This cohort achieved a mean of 9.8 years of formal education with 16% achieving <7 years (elementary level) of education. 52.8% of the participants were married. The mean BMI was overweight at 27.7 kg/m^2 with almost half (49.0%) of participants with a BMI >25 kg/m^2. Over one-third (38.0%) of participants were current or former smokers. 11.5% had a clear history of acute MI at baseline or over the following 5 years. Likewise, the history of diabetes mellitus and cancer were 12.6% and 16.5% respectively over this same time period. These finding are summarized in Figure 4.

Figure 4: Characteristics of Study Cohort*



* Characteristics at blood draw (follow-up 6), except as noted
† Does not include E. Boston (n=1248), race was not collected
‡ Reported at baseline interview

Blood values broken down by ATP III guidelines are also presented in Figure 4. The mean HDL-C was 48.3 (± 15.3) mg/dL with 52.07% of the cohort meeting our criteria for low HDL-C, which was 50 mg/dL in women and 40mg/dL in men. Similarly, half (50.36%) our cohort met our criteria of ideal triglycerides <150 mg/dL with a mean value of 179.3 (± 111.8) mg/dL. Very few (3.78%) met our criteria for renal insufficiency (BUN >40 mg/dL or creatnine >2mg/dL) with mean values of BUN of 19.9 (± 8.0) mg/dL and creatinine 1.3 (± 2.0) mg/dL. glucose of 125.4 (± 56.4). Though not included in the final model due to its lack of predictive value, mean total cholesterol was elevated at 214.2 (± 43.3) mg/dL. A summary of these serum values and others is provided in Table 5.

Table 5: EPESE Serum Values by Site

LAB VALUES	E. Boston (N=1248)		Iowa (N=1939)		New Haven (N=997)		Total (N=4184)	
	n	Mean (±SD)	n	Mean (±SD)	n	Mean SD	n	Mean
TRIGLYCERIDES	1211	184.5 (±110.94)	1931	179.8 (±117.73)	975	171.0 (±111.29)	4117	178.4
CHOLESTEROL	1216	214.0 (±42.81)	1934	215.8 (±44.00)	983	214.9 (±44.11)	4133	214.9
HDL-C	1215	46.5 (±14.79)	1934	49.3 (±14.69)	979	48.5 (±14.70)	4128	48.1
WBC	1152	7.0 (±2.19)	1928	6.4 (±2.57)	866	6.7 (±2.71)	3946	6.7
HGB	1152	13.4 (±1.50)	1928	14.2 (±1.48)	866	13.4 (±1.65)	3946	13.7
HCT	1152	40.5 (±4.40)	1928	42.7 (±4.40)	866	40.9 (±4.81)	3946	41.4
PLATELETS	1102	255.3 (±75.57)	1901	251.2 (±89.69)	840	269.1 (±87.21)	3843	258.5
SODIUM	1212	139.2 (±7.04)	1932	140.5 (±4.50)	974	139.7 (±5.44)	4118	139.8
POTASSIUM	1212	4.3 (±0.47)	1932	4.7 (±0.56)	974	4.4 (±0.59)	4118	4.5
CHLORIDE	1212	101.8 (±6.20)	1932	102.7 (±4.55)	974	101.5 (±5.40)	4118	102.0
BICARBONATE	1211	28.2 (±4.49)	1932	29.8 (±4.56)	975	34.9 (±6.94)	4118	31.0
BUN	1212	20.4(±7.84)	1932	19.7 (±7.27)	975	20.5 (±8.57)	4119	20.2
CREATININE	1212	1.4 (±4.27)	1932	1.2 (±0.36)	975	1.3 (±1.01)	4119	1.3
GLUCOSE	1212	133.3 (±61.91)	1932	119.6 (±49.14)	975	124.0 (±56.08)	4119	125.6

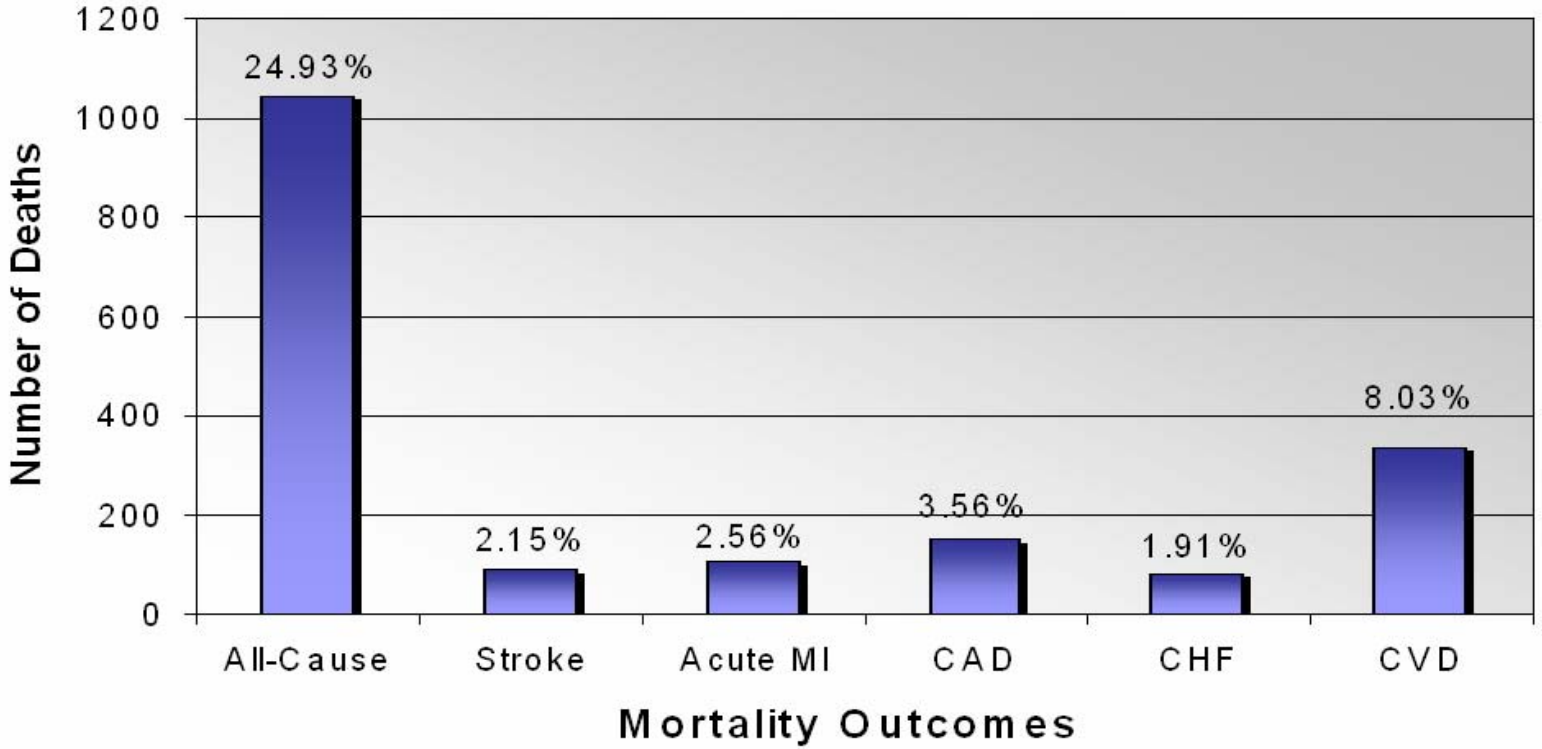
Outcomes

The distribution of the causes of death was similar in the EPESE cohort with serum samples as in the whole EPESE population. Table 6 and Figure 5 illustrate observed 5-year mortality by different conditions. The specific mortality outcomes of AMI, CAD, CHF and stroke accounted for almost 40% of the deaths during the five years of follow-up of both the cohort with serum samples (39.6%) and the entire EPESE population (39.7%). Cardiovascular mortality including AMI, CAD, and CHF accounted for 471 deaths (7.9% mortality) or 31.4% of all deaths (n=1509) in the cohort with serum samples. Stroke accounted for an additional 123 deaths (2.1% mortality) or 8.2% of all deaths in this group.

Table 6: Study Cohort vs. Full EPESE 5yr Mortality by Cause of Death

5 Year Mortality by Cause of Death, n (%)	**Study Cohort**				**Full EPESE (n=14456)**
	E. Boston (n=1248)	**Iowa (n=1939)**	**New Haven (n=997)**	**Total (n=4184)**	
All Cause	288 (23.1%)	487 (25.1%)	268 (26.9%)	1043 (24.9%)	3492 (24.2%)
Stroke	17 (1.4%)	52 (2.7%)	21 (2.1%)	90 (2.2%)	266 (1.8%)
Acute MI	32 (2.6%)	56 (2.9%)	19 (1.9%)	107(2.6%)	477 (3.3%)
CAD	36 (2.9%)	81 (1.4%)	32 (3.2%)	149 (3.6%)	407 (2.8%)
CHF	26 (2.1%)	41 (2.1%)	13 (1.3%)	80 (1.9%)	235 (1.6%)

Figure 5: EPESE 5-Year Mortality by Cause of Death



Key:

Percentage above the bars represents % mortality of cohort from that outcome

Acute MI= Acute Myocardial Infarction

CAD= Coronary Artery Disease (not AMI)
CHF= Congestive Heart Failure
CVD= Total combined mortality from Acute MI, CAD, and CHF

Figure 6 shows the breakdown of this mortality by low and high HDL-C levels. Table 6 shows unadjusted results based on the Cox proportional hazards models. An HDL-C of ≤ 50 mg/dL in women and ≤ 40 in men was not significantly associated with crude all-cause (P=.413), AMI (P=.473), CHF (P=.259), and stroke (P=.345) mortality. HDL-C was significantly associated with unadjusted CAD (P=.033) mortality. However, following adjustment for demographic, clinical, and functional covariates, the adjusted hazard ratios (HR) was no longer statistically significant or suggestive of any trend for all-cause (HR=1.03, 95% CI 0.90-1.18), AMI (HR=1.09, 95% CI 0.70-1.71), CAD (HR=1.33, 95% CI 0.91-1.92), CHF (HR=1.07, 95% CI 0.63-1.81) and stroke (HR=0.80, 95% CI 0.51-1.27) mortality. The adjusted results are presented in Table 7. HDL-C was the only serum value of interest not significantly associated with unadjusted all-cause mortality as shown in Table 6.

Figure 6: All-Cause and Cardiovascular Mortality by Cause of Death by High and Low HDL-C

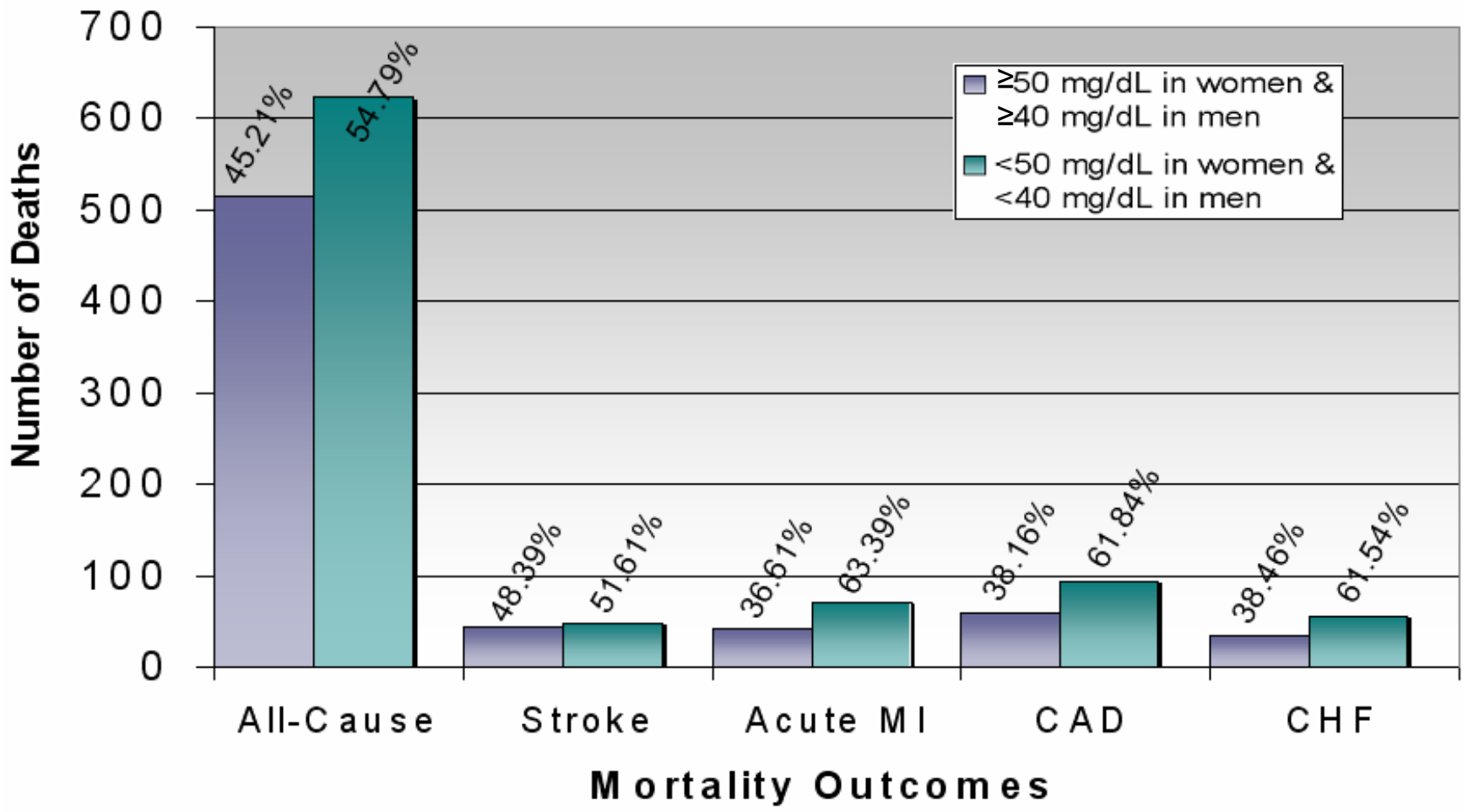


Table 6: Unadjusted 5-Year Cardiovascular, Stroke, & All-Cause Mortality

UNADJUSTED Hazard Ratios (95% Confidence Intervals) and P-Values

Serum Values (mg/dL)	AMI	CAD (not AMI)	CHF	Stroke	All Cause
HDL-C Female <50 & Male <40	1.17 (0.76-1.80) P=.473	1.48 (1.03-2.13) P=.033	1.34 (0.81-2.21) P=.259	0.80 (0.51-1.27) P=.345	1.06 (0.92-1.21) P=.413
LDL <200	1.09 (0.72-1.63) P=.689	1.51 (1.07-2.11) P=.018	0.84 (0.52-1.35) P=.461	1.22 (0.78-1.90) P=.383	1.51 (1.33-1.72) P=.001
Triglycerides <150	0.57 (0.36-0.90) P=.015	1.37 (0.96-1.96) P=.085	1.51 (0.92-2.46) P=.101	0.70 (0.44-1.12) P=.138	1.17 (1.02-1.34) P=.025
BUN >40 or Cr >2	2.69 (1.35-5.38) P=.005	2.63 (1.45-4.79) P=.002	8.25 (4.68-14.55) P<.001	3.56 (1.71-7.44) P=.001	3.41 (2.76-4.22) P<.001
Glucose <110	2.12 (1.41-3.18) P<.001	1.53 (1.10-2.12) P=.012	2.23 (1.39-3.57) P=.001	1.10 (0.72-1.68) P=.648	1.41 (1.24-1.59) P<.001

Table 7: Adjusted 5-Year Cardiovascular, Stroke, & All-Cause Mortality

ADJUSTED Hazard Ratios (95% Confidence Intervals) and P-Values					
Serum Values (mg/dL)	AMI	CAD (not AMI)	CHF	Stroke	All Cause
HDL-C Female <50 & Male <40	1.09 (0.70-1.71) P=.697	1.33 (0.91-1.92) P=.137	1.07 (0.63-1.81) P=.806	0.74 (0.46-1.18) P=.204	1.03 (0.90-1.18) P=.694
LDL <200	0.68 (0.44-1.01) P=.083	1.18 (0.83-1.70) P=.359	0.53 (0.32-0.91) P=.020	0.96 (0.60-1.54) P=.867	1.08 (0.94-1.24) P=.261
Triglycerides <150	0.63 (0.40-1.00) P=.049	1.35 (0.93-1.95) P=.113	1.35 (0.81-2.26) P=.253	0.73 (0.46-1.19) P=.206	1.19 (1.03-1.36) P=.017
BUN >40 or Cr >2	1.34 (0.65-2.77) P=.427	1.55 (0.83-2.90) P=.167	4.49 (2.40-8.38) P<.001	2.02 (0.94-4.33) P=.071	2.04 (1.63-2.54) P<.001
Glucose <110	1.83 (1.22-2.81) P=.004	1.29 (0.91-1.81) P=.152	1.63 (0.99-2.67) P=.053	1.00 (0.64-1.55) P=.990	1.22 (1.08-1.39) P=.002

An LDL-C of <200 mg/dL was significantly associated with increased crude all-cause (P<.001) and CAD (P=.018) mortality. Following adjustment our covariates, the adjusted HR for CAD was no longer statistically significant (HR=1.18, 95% CI 0.83-1.70). The LDL-C adjusted HR for decreased CHF mortality was now significant (p= .020, HR=0.53, 95% CI 0.32-0.91). LDL-C and HDL-C were the only two serum values of interest that were not significantly associated with adjusted all-cause mortality.

Impaired renal function indicated by a BUN >40 mg/dL or creatinine >2 mg/dL was significantly associated with crude all-cause (P<.001), AMI (P=.005), CAD (P=.002), CHF (P<.001), and stroke (P=.001) mortality. Following adjustment our covariates, it remained significant with P<0.001 for both CHF (HR=4.49, 95% CI 2.40-8.38) and all-cause (HR=2.04, 95% CI 1.63-2.54) mortality. The association between increased risk of CHF and all-cause mortality with impaired renal function is expected in light of the effect of renal function on CHF severity and its indication of overall poor health and comorbidity (96,97).

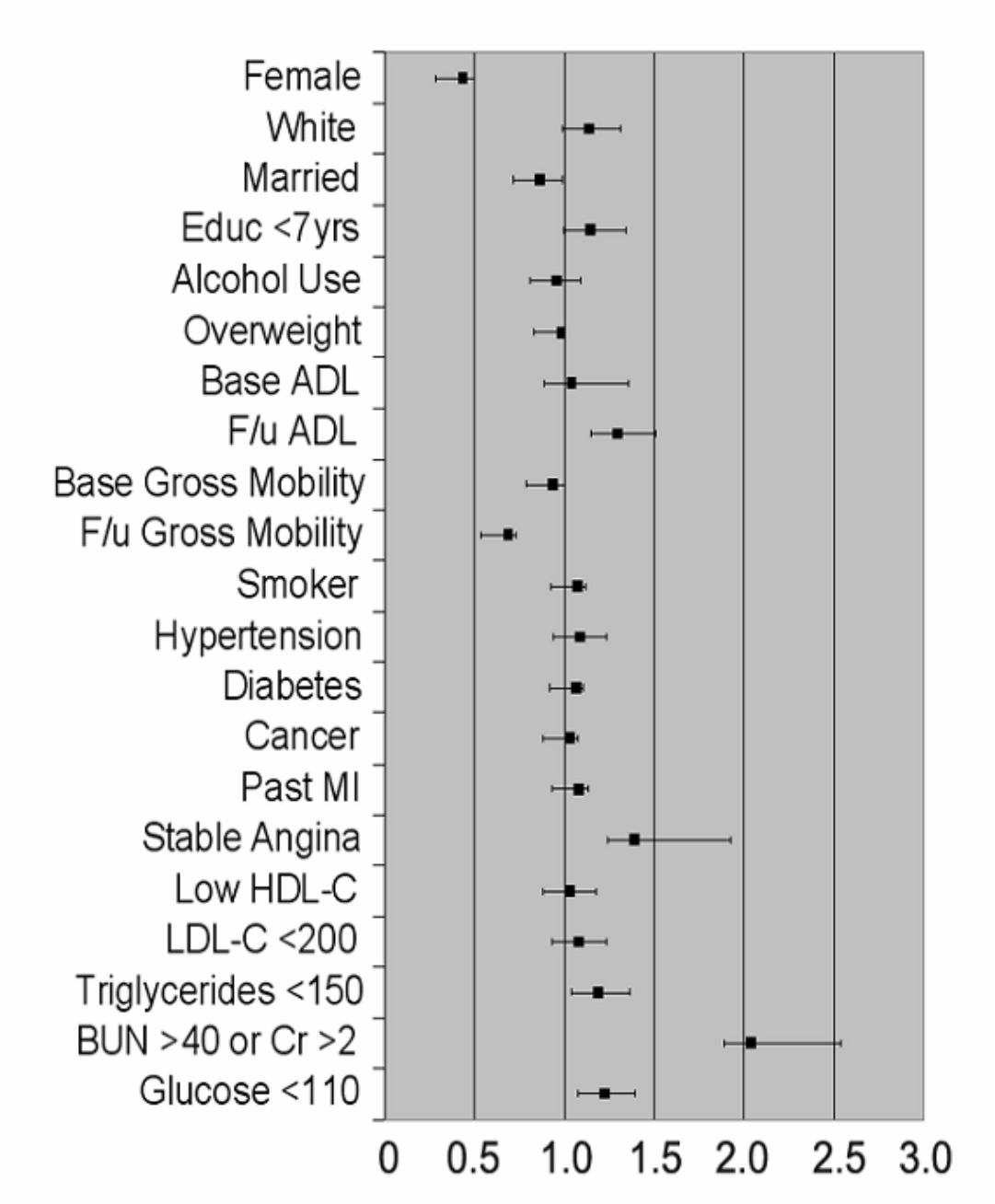
Impaired glucose tolerance glucose indicated by a glucose value >110 mg/dL was significantly associated with crude all-cause

(P<.001), AMI (P<.001), CAD (P=.012), and CHF (P<.001) mortality. Following adjustment our covariates, it remained significant for both increased AMI (HR=1.85, 95% CI 1.22-2.81) and all-cause (HR=1.22, 95% CI 1.08-1.39) mortality and very close to significant in CHF (p=.053) mortality. Similarly, ideal triglyceride levels of <150 mg/dL were significantly associated with both unadjusted and adjusted AMI and all-cause mortality. Likewise, the relationship between elevated glucose and AMI and all-cause mortality is unsurprising (98). A similar relationship is also present with elevated triglycerides. The mortality risks associated with elevated glucose and triglycerides could possibly related to the effects of metabolic syndrome in an older population (99), but documented fasting blood draws and waist-to-hip measurements are necessary to draw a conclusion between these factors since both these blood values are highly influences by the fasting vs. non-fasting state.

With respect to specific mortality outcomes, both CAD and stroke mortality lacked any significant association with any serum value. AMI was significantly associated with triglycerides and glucose, while BUN or creatinine was associated with CHF. All three (triglycerides, glucose and BUN or creatinine) were significantly associated with all-cause mortality.

When examining the hazard ratios for all of our covariates, it becomes clear that factors beyond blood values are very important predictors of mortality (Figure 5). Obviously, age, sex, and BMI are significant considerations, but gross mobility and basic functional status including performance of ADLs are also significant predictors of mortality.

Figure 5: All Cause Mortality Hazard Ratios with 95% Confidence Intervals for Model Variables



CHAPTER 5: DISCUSSION

Laboratory research has taught us that HDL-C has a complex regulatory relationship to other plasma lipids and the vascular endothelium itself (4,13). Epidemiological research has shown us the prospect of its use as a means of risk stratification (2,20-22). It seems an obvious choice for mortality predictions, yet following adjustment for demographic, clinical, and functional covariates, there was no relationship between low HDL-C levels defined by current ATP III guidelines (<50 mg/dL in women and <40 mg/dL in men) and increased risk of 5-year cardiovascular, stroke or all-cause mortality among this cohort of older adults. Even prior to full adjustment, the statistical significance of HDL-C levels stratified by current guidelines were not significantly predictive of cardiovascular or all-cause mortality with the exception of CAD (not AMI). This finding leaves us with several new questions with regard to appropriate lipid levels for risk stratification and guidelines for management of older adult patients. We will examine the reason why HDL-C may lose predictive value in this cohort of older community-dwelling adults. We will also explore the unique characteristics of this cohort and extrapolate what our findings would mean for the patient presenting in clinic today. Lastly, we will look at the framework for future study of HDL-C in older adults.

Findings in primarily middle age cohorts have helped to define the current lipid profile guidelines, which we use as a yardstick for management in all our patients regardless of age. In all areas of medicine, it is becoming more apparent that such epidemiologic study findings cannot be simply and broadly applied across both sexes and all age ranges. This may also ring true with regard to HDL-C level and older patients for several reasons. Since the elderly face competing mortality risks from co-morbidities and potential future illness, HDL-C alone may have minimal effect on future longevity (100). Studies examining the lipid profiles in an elderly cohort of offspring of centenarians show a difference in lipid profiles with significantly decreased LDL levels and higher, but not significant HDL-C levels (101). In light of this, numerous other environmental and genetic factors related to longevity may play a greater role either by affecting the ratio of anti-inflammatory to pro-inflammatory HDL-C or by some other interaction with plasma lipids. Without dismissing the value of HDL-C in a middle-aged cohort, we should reconsider the role of HDL-C as a marker of the origination of arteriosclerosis and development of cardiovascular disease in a population set to have their initial event. In this context HDL-C would not necessarily exhibit a major predictive value in an older population with many other competing mortality risks.

Likewise, both acute and chronic systemic illness and inflammation, which may not always be recognized, can also play an important role in the progression of cardiovascular disease placing HDL-C in a setting where it may behave paradoxically to feed into this cycle rather than protect (4,11,14-17). For example, higher-functioning and more-mobile older adults as represented by this study's cohort typically have higher HDL-C levels, which are negatively correlated with visceral adiposity (suggestive of metabolic syndrome) compared to their non-community dwelling age-matched counterparts who have lower HDL-C levels showing no relationship to their waist girth (71,72). Therefore, in choosing individuals capable of living independently, there is the inherent limitation of selecting those in better general health with potentially better though not necessarily "ideal" lipid profiles as compared to their institutionalized counterparts who are more likely affected by chronic illness. Through the selection of a more mobile cohort, we must accept that this sample does not represent all older adults, but does provide the benefit of representing the patient naïve to lipid-lowering medications who might walk into a clinician's office where the decision point of whether or not to implement lipid therapy ultimately occurs.

In fact, a unique characteristic of this cohort is that they have not been treated with lipid-lowering therapies. It is likely that for this reason, the majority of this study's cohort also has an elevated LDL ≥200 mg/dL (60.9%). Today such a level will automatically warrant the use of a statin based on the ATP III guidelines to treat LDL-C ≥100 mg/dL without even accounting for lower recommendations for that subset of patients with a prior history of cardiovascular disease (those with angina and/or previous MI) who would be treated if ≥70 mg/dL. For this reason, our study presents a somewhat artificial circumstance with regard to current treatment guidelines and goals. Even with this limitation, the lack of association found between LDL <200 mg/dL and all-cause, stroke and most cardiovascular outcomes presents an interesting question in itself. This lack of significance may be due to the choice of a high cut-off point going along with the evidence supporting current lower guidelines and with more recent evidence suggesting even more aggressive statin use to lower the LDL-C to around 70 mg/dL in those at greatest risk for cardiovascular events (2,75). However, even with higher dose statin regimens, the decreased LDL-C achieved is only significantly related to the occurrence of new major cardiovascular event, but did not have any effect on overall mortality (75,77). The effect of LDL-C

may be less dramatic when examined against longer term mortality and outside of the context of the various additional anti-inflammatory benefits attributed to statin use, which was minimal (approximately 1%) within this study cohort (54). In one sense, the decision to treat a patient similar to our cohort to minimize morbidity related to cardiovascular disease may be clear with regard to their elevated LDL-C, but it is less clear on whether it is worth treating a low HDL-C, which would likely mean the use of multiple agents.

Polypharmacy is a common situation and often a complaint in the elderly; thus, it is important that we consider this issue when making treatment decisions in this population. In addition to the sometimes complicated logistics and financial burden of taking multiple medications, there are the problems of drug interactions and paradoxical reactions related to impaired clearance due to changes in liver and renal function and differences in the volume distribution due to decreasing muscle mass. Yet, it is important to tread this slippery slope carefully because failure to prescribe a drug with potential morbidity and/or mortality benefits for cursory reasons is just as hazardous. To treat an increased LDL-C, patients regardless of age are often put on statin drugs, which do little to

affect HDL-C levels. Various studies have shown benefits of secondary prevention in adults over 65 years of age when treated with a statin including the prospective PROSPER, as well as subgroup analysis of older adults in CARE, 4S, and LIPID trials (102-105). Unfortunately, data in the form of clinical trials regarding primary prevention in this population is notably lacking. Nonetheless, in the setting of a positive risk-benefit analysis, the evidence for treating an elevated LDL-C with a statin remains favorable in older adults without some other contraindication to therapy.

If a physician chooses to treat a lower HDL-C level, the addition of a fibrate or niacin derivative would be the next course of action. No clinical trials focusing on the concurrent use of statins and fibrates have been done exclusively in an elderly population, but literature reviews of cohorts including these patients have shown no significant increased risks (106). However, increased age, female gender, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise increased risk for myopathy when these drug classes are used concurrently (106).

Clinical trials including older adults have also looked at statins and niacin for secondary prevention in cardiovascular disease looking at several measures. The ARBITER 2 trial had a primary outcome examining carotid intimal thickening in those with known cardiovascular disease following treatment with 1g of niacin in addition to a statin regimen (62). Intimal thickening was significantly reduced in the dual treatment group and HDL-C levels were higher with no adverse events different from placebo (62). Even though not in an exclusively elderly population, the mean age was 67 years ±10 years. Another study also showed an increase in HDL-C on both drugs, but revealed no change in the plaque calcification or progression between statin and statin-niacin groups (107). So, HDL-C is elevated significantly with niacin though measurable effects on arteriosclerosis have not been found. But, there also has not been an increase in side effects and extended release formulations have been better tolerated with regard to flushing, so the theoretical benefit comes with very little tangible risk. Just as with fibrates, there is a lack of clinical trials performed specifically in an older population. So, the clinician must extrapolate data from one population to another weighing risks and benefits obtained primarily from subgroups analysis and literature reviews in an effort to isolate adults over 65 years of age.

In the coming decades, we are facing a major shift that will affect the economics and practice of healthcare as we tackle the problems of an aging population. We are also a society plagued by a deadly triad of obesity, diabetes, and cardiovascular disease, which only threaten to reach new heights. For these reasons, it is important to continue to refine the process of risk stratification and implement the appropriate interventions, pharmacologic or otherwise to decrease the morbidity and mortality associated with cardiovascular disease. To do this, medicine as a profession and to a great degree society itself has embraced evidence-based medical practice. This has helped us create guidelines for practice that have in turn improved the delivery of the best known standard of care to greater numbers of patients.

Our research aim was to test current guidelines and examine the relationship between untreated HDL-C levels below the recommended level of <50 mg/dL in women and <40 mg/dL in men on five year cardiovascular, stroke, and all-cause mortality in community-dwelling adults over 71 years of age. Using these current recommended HDL-C levels clinically as a deciding factor for initiating aggressive lipid-lowering therapy in those without other

clear indications to reduce 5-year mortality is most likely not useful in those over 70 years of age. However, there remain numerous gaps in the treatment of cardiovascular disease, which will need to be addressed in coming years. These gaps will be filled in the laboratory to further explore the complex physiology of HDL-C and its interactions with other plasma lipids. Likewise, they will need to be filled by clinical research focusing on those older adults who remain those with both the greatest risk and the potential for the greatest benefit. Until then, we must examine and re-examine those guidelines and goals we set to see if they do indeed match the patient sitting before us. In essence, that was the aim of this project and ultimately it is what physicians have always done--practice the art of medicine by utilizing careful clinical judgment in the face of what will always be limited evidence.

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APPENDIX 1: EPESE Questions for Variables

DEMOGRAPHIC VARIABLES

Sex: 1.6 Sex 1 = Male 2 = Female

Race: 1.7 Race (Not East Boston)

1 = White 3 = Other

2 = Black Blank

Age: 2.2 Calculated age at time of interview Years

Education: 2.17 What is the highest grade or year of regular school you have completed? Year

Marital Status: 2.18 Have you ever been married?

1 = Yes 2 = No

2.19 Are you now married, separated, divorced or widowed? Are you now married, widowed, divorced or separated?

1 = Married
2 = Separated
3 = Divorced
4 = Widowed
5 = Annulled

CLINICAL VARIABLES

Cancer History: 29.18 Has a doctor ever told you that you had a cancer, malignancy or malignant tumor of any type? 1=Yes 2=Suspect 3=no

Diabetes History: 29.41 Has a doctor ever told you that you had diabetes, high blood sugar, or sugar in your urine? 1=Yes 2=Suspect 3=No

Antihypertensive: 29.60 Are you currently taking any medications for your high blood pressure? 1=Yes 2=No

Angina:	34.18 Do you get this pain when you hurry or walk uphill?	1=Yes 2=No 3=Never walks uphill
Myocardial Infarction :	29.1 Have you ever been told by a doctor that you had a heart atttack, coronary, coronary thrombosis, coronary occlusion, or myocardial infarction?	1=Yes 2=Suspect 3=No

FUNCTIONAL VARIABLES

Cognitive Status: (Short Portable Mental Status Questionnaire)

19.1	How old are you?	1 = Correct 2 = Incorrect
19.2	When were you born?	1 = Correct 2 = Incorrect
19.3	What is the date today?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)
19.4	What day of the week is it?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)
19.5	Who is the president of the U.S. (now)?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)
19.6	Who was (the) president (just) before him?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)
19.7	What was (is) your mother's maiden name?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)
19.8	What is your telephone number?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston) 4 = No telephone (NHaven & EBoston)
19.9	What is your (street) address?	1 = Correct 2 = Incorrect 3 = Correct with aid (EBoston)

Gross Mobility:

20.32	Are you able to do heavy work around the house like (shoveling snow), washing windows, walls or floors without help (from another person)?	1 = Yes 2 = No
20.33	Are you able to walk up and down stairs to the second floor without help (from another person)?	1 = Yes 2 = No
20.34	Are you able to walk half a mile without help (from another person)? That's about 8 ordinary blocks.	1 = Yes 2 = No

Physical Performance Difficulties

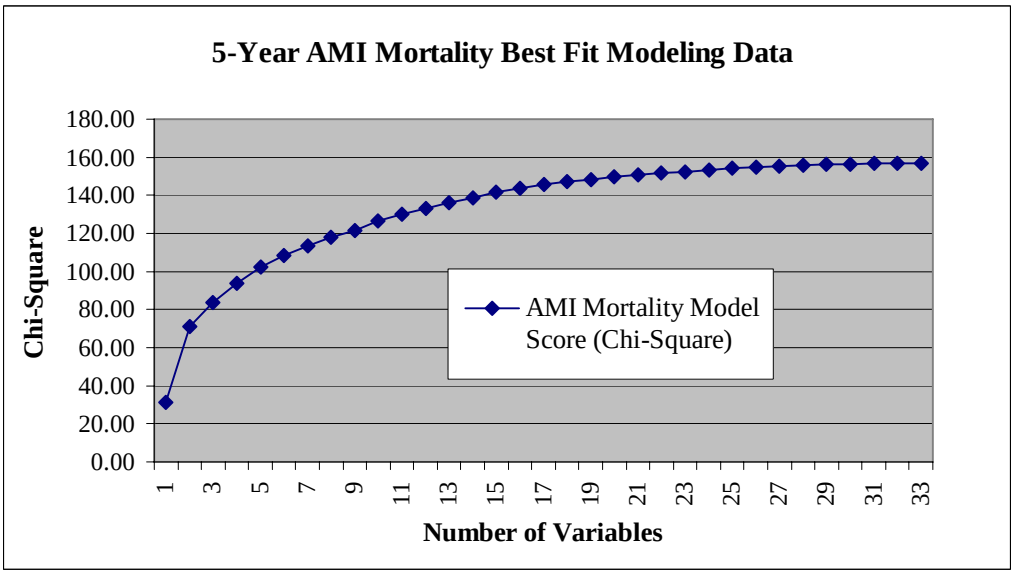
20.39	How much difficulty, if any, do you have pulling or pushing large objects like a living room chair?	1 = No difficulty at all 2 = little/some difficulty 3 = A lot of difficulty 4 = Just unable to do it
20.40	What about stooping, crouching, or kneeling?	1 = No difficulty at all 2 = little/some difficulty 3 = A lot of difficulty 4 = Just unable to do it
20.43	Reaching or extending arms above shoulder level?	1 = No difficulty at all 2 = little/some difficulty 3 = A lot of difficulty 4 = Just unable to do it
20.44	Either writing or handling (or fingering) small objects?	1 = No difficulty at all 2 = little/some difficulty 3 = A lot of difficulty 4 = Just unable to do it

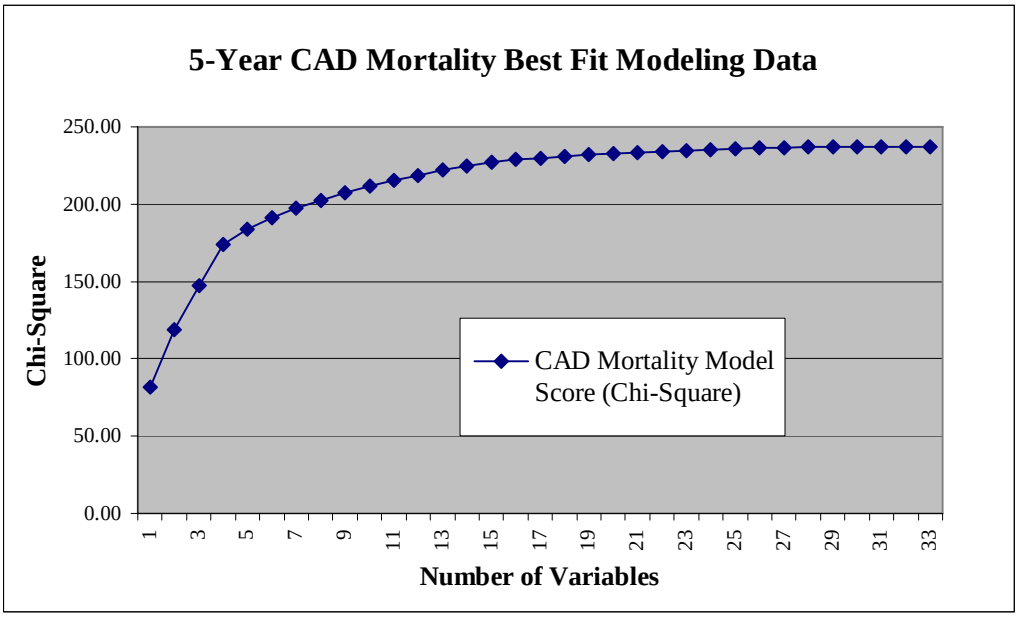
APPENDIX 2: EPESE Blood Values

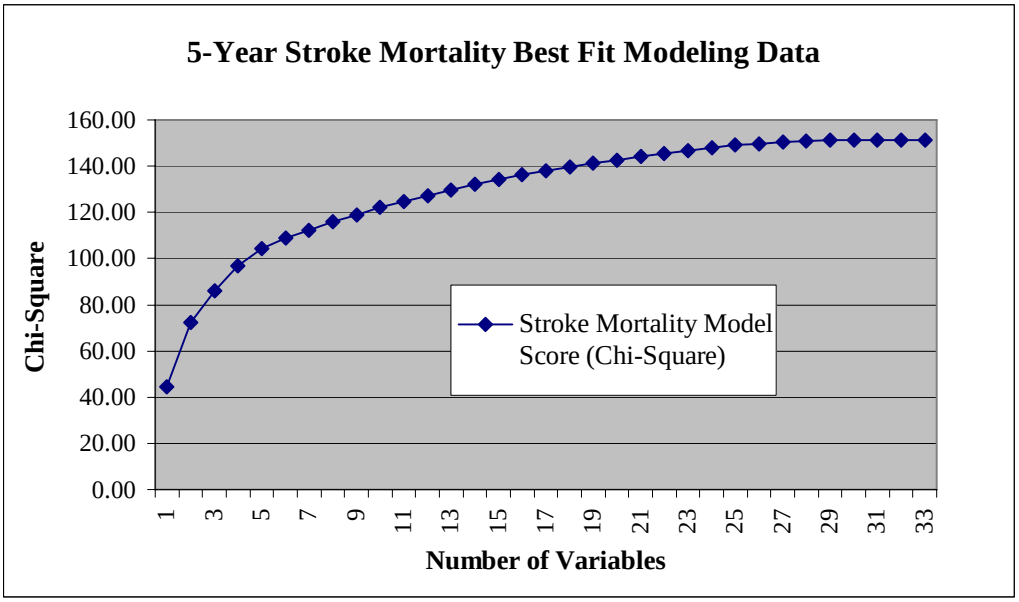
Laboratory Tests	East Boston (N=1248)		Iowa (N=1939)		New Haven (N=997)		Total (N=4184)	
	n	Mean (±SD)	n	Mean (±SD)	N	Mean (±SD)	n	Mean
WBC	1152	7.0 (±2.2)	1928	6.4 (±2.6)	866	6.7 (±2.7)	3946	6.7
RBC	1152	4.4 (±0.5)	1928	4.6 (±0.5)	866	4.5 (±0.5)	3946	4.5
HEMOGLOBIN	1152	13.4 (±1.5)	1928	14.2 (±1.5)	866	13.4 (±1.6)	3946	13.7
HEMATOCRIT	1152	40.5 (±4.4)	1928	42.7 (±4.4)	866	40.9 (±4.8)	3946	41.4
MCV	1152	91.5 (±6.5)	1928	93.7 (±5.3)	866	92.1 (±6.0)	3946	92.4
MCH	1152	30.3 (±2.4)	1928	31.1 (±1.9)	866	30.2 (±2.2)	3946	30.5
MCHC	1152	33.1 (±0.7)	1928	33.2 (±0.8)	866	32.8 (±0.9)	3946	33.0
RBC WIDTH	1152	14.4 (±1.7)	1550	15.0 (±1.9)	866	15.1 (±2.0)	3568	14.9
PLATELETS	1102	255.3 (±75.6)	1901	251.2 (±89.7)	840	269.1(±87.2)	3843	258.5
NEUTROPHILS	1102	60.3 (±10.6)	1707	63.2 (±9.6)	811	61.7 (±10.1)	3620	61.7
BANDS	973	0.4 (±1.0)	1387	0.2 (±0.8)	660	0.2 (±0.7)	3020	0.3
LYMPHOCYTES	1102	33.8 (±10.5)	1707	32.5 (±9.5)	811	33.8 (±9.9)	3620	33.3
MONOCYTES	1088	3.2 (±2.2)	1652	2.5 (±2.1)	795	2.5 (±2.5)	3535	2.7
EOSINOPHILS	1058	2.0 (±2.0)	1651	1.7 (±1.7)	777	1.9 (±2.1)	3486	1.9
BASOPHILS	965	0.3 (±0.6)	1414	0.2 (±0.5)	671	0.2 (±0.4)	3050	0.2
GLUCOSE	1212	133.3 (±61.9)	1932	119.6 (±49.1)	975	124.0 (±56.1)	4119	125.6
BUN	1212	20.4 (±7.8)	1932	19.7 (±7.3)	975	20.5 (±8.6)	4119	20.2
CREATININE	1212	1.4 (±4.3)	1932	1.2 (±0.4)	975	1.3 (±1.0)	4119	1.3
URIC ACID	1212	6.2 (±2.0)	1932	6.3 (±1.7)	974	6.4 (±1.7)	4118	6.3
SODIUM	1212	139.2 (±7.0)	1932	140.5 (±4.5)	974	139.7 (±5.4)	4118	139.8
POTASSIUM	1212	4.3 (±0.5)	1932	4.7 (±0.6)	974	4.4 (±0.6)	4118	4.5
CHLORIDE	1212	101.8 (±6.2)	1932	102.7 (±4.6)	974	101.5 (±5.4)	4118	102.0
BICARBONATE	1211	28.2 (±4.5)	1932	29.8 (±4.6)	975	34.9 (±6.9)	4118	31.0

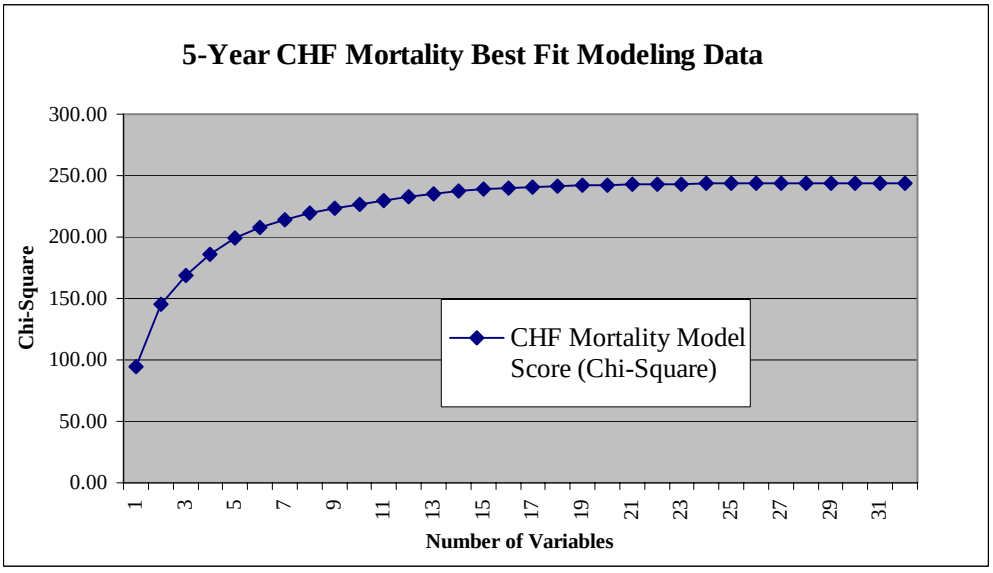
Laboratory Tests	East Boston (N=1248)		Iowa (N=1939)		New Haven (N=997)		Total (N=4184)	
	n	Mean (±SD)	n	Mean (±SD)	N	Mean (±SD)	n	Mean
TOTAL PROTEIN	1212	7.1 (±6.0)	1932	6.8 (±0.5)	975	6.9 (±0.7)	4119	6.9
ALBUMIN	1211	4.1 (±1.0)	1932	4.1 (±0.3)	975	4.0 (±0.3)	4118	4.1
CALCIUM	1211	9.5 (±0.7)	1932	9.5 (±0.5)	975	9.5 (±1.4)	4118	9.5
PHOSPHATE	1211	3.7 (±3.9)	1932	3.6 (±0.5)	975	3.5 (±0.5)	4118	3.6
LDH	1210	156.9 (±48.2)	1932	175.6 (±40.2)	975	162.7 (±43.0)	4117	165.1
SGOT	1210	16.6 (±13.5)	1931	17.4 (±9.6)	975	16.4 (±18.5)	4116	16.8
GGT	1211	26.8 (±36.0)	1932	24.2 (±41.7)	975	25.8 (±33.4)	4118	25.6
ALKALINE PHOSPHATASE	1211	101.8 (±72.0)	1932	98.1 (±53.0)	975	118.5 (±229.0)	4118	106.1
TOTAL BILIRUBIN	1211	0.4 (±0.3)	1932	0.4 (±0.2)	975	0.4 (±0.3)	4118	0.4
CHOLESTEROL (SMA)	1211	216.0 (±42.9)	1932	217.4 (±42.1)	975	213.7 (±43.7)	4118	215.7
TRIGLYCERIDES	1211	184.5 (±110.9)	1931	179.8 (±117.7)	975	171.0 (±111.3)	4117	178.4
IRON	1211	79.5 (±29.3)	1932	85.8 (±29.8)	974	76.0 (±28.6)	4117	80.4
GLOBULIN	1211	3.1 (±8.3)	1932	2.7 (±0.4)	975	2.9 (±1.1)	4118	2.9
ALBUMIN/GLOBULIN RATIO	1211	1.5 (±1.4)	1932	1.5 (±0.3)	974	1.5 (±0.3)	4117	1.5
BUN/CREATININE RATIO	1209	17.4 (±4.8)	1932	16.6 (±4.9)	974	17.0 (±5.7)	4115	17.0
CHOLESTEROL	1216	214.0 (±42.8)	1934	215.8 (±44.0)	983	214.9 (±44.1)	4133	214.9
HDL CHOLESTEROL	1215	46.5 (±14.8)	1934	49.3 (±14.7)	979	48.5 (±14.7)	4128	48.1
DHEAS	1225	0.5 (±0.4)	nc	nc	Nc	nc	1225	0.5
HEMOGLOBIN A1C	1221	6.3 (±1.3)	1698	5.7 (±1.2)	Nc	nc	2919	6.0

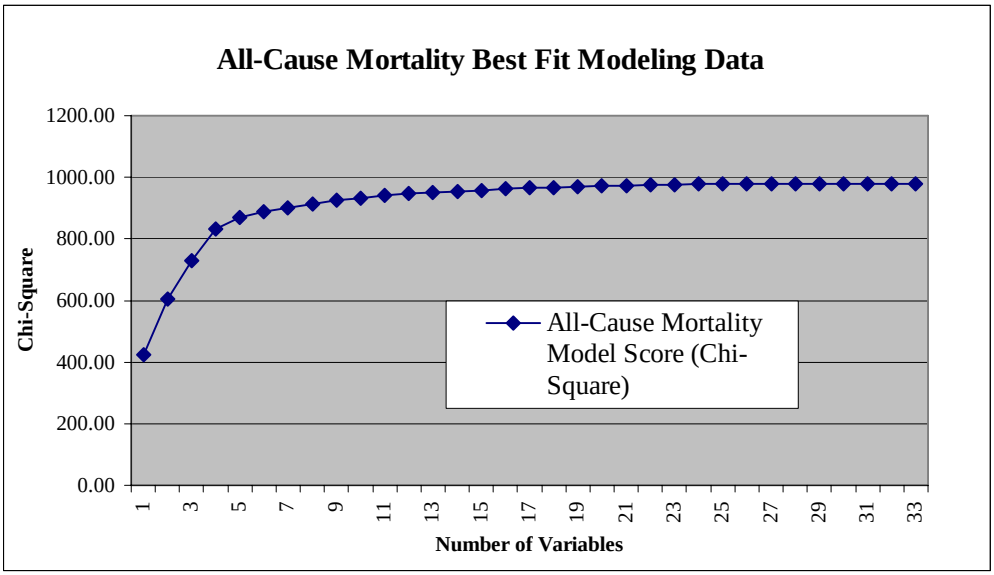
APPENDIX 3: Chi-Square Best-Fit Modeling






5-Year Stroke Mortality Best Fit Modeling Data
Chi-Square
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
Number of Variables
Stroke Mortality Model Score (Chi-Square)


5-Year CHF Mortality Best Fit Modeling Data
Chi-Square
300.00
250.00
200.00
150.00
100.00
50.00
0.00
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
Number of Variables
CHF Mortality Model Score (Chi-Square)


All-Cause Mortality Best Fit Modeling Data
1200.00
1000.00
800.00
600.00
400.00
200.00
0.00
Chi-Square
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
Number of Variables
All-Cause Mortality Model Score (Chi-Square)

Best Subset (p=0.05) 5-year All Cause Mortality Cox proportional Hazards Regression Model

The PHREG Procedure

Regression Models Selected by Score Criterion

# of Variables	Score Chi-Square	Variables Included in Model
1	424.8006	GrossMobilityBase_6
1	299.0994	age_6
1	178.1457	BUN_Gr_40_OR_Creat_Gr_2
2	603.8073	GrossMobilityBase_6 Female
2	559.1845	GrossMobilityBase_6 BUN_Gr_40_OR_Creat_Gr_2
2	537.9685	GrossMobilityBase_6 age_6
3	728.1566	GrossMobilityBase_6 Female age_6
3	715.6414	GrossMobilityBase_6 Female BUN_Gr_40_OR_Creat_Gr_2
3	666.3973	GrossMobilityBase_6 age_6 BUN_Gr_40_OR_Creat_Gr_2
4	833.6088	GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
4	763.4625	ADLscorebase_6 GrossMobilityBase_6 Female age_6
4	754.0138	pulse_10 GrossMobilityBase_6 Female BUN_Gr_40_OR_Creat_Gr_2
5	870.1502	ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
5	852.2660	pulse_10 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
5	847.9079	BP_D_Ls_90_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
6	888.8593	pulse_10 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
6	884.8292	DM_score ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
6	881.5548	BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2

7	901.9492	DM_score pulse_10 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
7	900.6105	HxAMI_score pulse_10 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
7	899.7256	pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
8	913.3662	DM_score HxAMI_score pulse_10 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
8	913.1660	DM_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
8	911.9676	HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
9	925.0698	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2
9	921.3095	HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Glucose_Gr_110
9	920.4280	DM_score HxAMI_score pulse_10 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150
10	932.2928	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150
10	931.0943	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2
10	930.9000	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Glucose_Gr_110
11	940.1858	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
11	937.6540	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150
11	937.5592	DM_score HxAMI_score Hx_Cu_Smoker_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150

12	946.1273	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
12	945.1906	DM_score HxAMI_score Hx_Cu_Smoker_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
12	943.9019	DM_score HxAMI_score HTN_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
13	951.5826	DM_score HxAMI_score Hx_Cu_Smoker_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
13	949.4635	DM_score HxAMI_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
13	949.4000	DM_score HxAMI_score HTN_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
14	955.2667	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
14	954.8939	DM_score HxAMI_score Hx_Cu_Smoker_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
14	954.7451	DM_score HxAMI_score Hx_Cu_Smoker_score ChxPain pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
15	958.4076	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
15	958.3946	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
15	958.3903	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
16	961.6841	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110

16	961.5998	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
16	961.4133	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
17	964.7687	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
17	963.9444	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
17	963.8255	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
18	967.0233	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
18	966.7581	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
18	966.7377	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
19	969.0675	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
19	968.9717	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110

19	968.8946	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200, BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
20	971.0972	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
20	970.9692	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
20	970.8880	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
21	973.0380	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
21	972.8801	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
21	972.7716	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
22	974.7774	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
22	974.7531	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
22	974.6717	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110

23	976.6861	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
23	976.0371	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
23	975.8508	DM_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
24	977.8364	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
24	977.3645	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
24	977.1638	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
25	978.5045	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
25	978.2845	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110

25	978.2538	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
26	978.9466	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
26	978.9069	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
26	978.7108	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
27	979.3576	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
27	979.0984	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110
27	979.0589	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 Glucose_Gr_110

28	979.4963	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
28	979.4564	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
28	979.4476	DM_score Canx_score HxAMI_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
29	979.6016	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
29	979.5784	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
29	979.5559	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110

30	979.6884	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
30	979.6634	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
30	979.6434	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
31	979.7559	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
31	979.692 2	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_S_Gr_160 BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
31	979.690 7	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use ADLscorebase GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110

32	979.7588	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_D_Ls_90 pulse_10 ETOH_use ADLscorebase GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
32	979.7585	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_S_Gr_160 BP_D_Ls_90 pulse_10 ETOH_use GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
32	979.6945	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_S_Gr_160 BP_D_Ls_90 pulse_10 ETOH_use ADLscorebase GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110
33	979.7613	DM_score Canx_score HxAMI_score DM_suspect_score Hx_Cu_Smoker_score HTN_score Obesity_score BP_Med ChxPain BP_S_Gr_160 BP_D_Ls_90 pulse_10 ETOH_use ADLscorebase GrossMobilityBase PPDscorebase SPMSQscorebase BP_S_Gr_160_6 BP_D_Ls_90_6 pulse_10_6 ADLscorebase_6 GrossMobilityBase_6 PPDscorebase_6 Female age_6 White Married Edu_Ls_7_year LDL_Ls_200 BUN_Gr_40_OR_Creat_Gr_2 Triglycerides_Ls_150 HDL_Ls_40_M_Ls_50_F Glucose_Gr_110

APPENDIX 4: Full Statistical Model Results

5-Year AMI Mortality Cox proportional Hazards Regression Model w/Blood

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	AMI5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	107	4077	97.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1755.888	1719.240
AIC	1755.888	1729.240
SBC	1755.888	1742.604

5-Year AMI Mortality Cox proportional Hazards Regression Model w/ Blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	36.6476	5	<.0001
Score	40.9020	5	<.0001
Wald	37.5295	5	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.08323	0.20777	0.1605	0.6887	1.087	0.723	1.633
BUN_Gr_40_OR_Creat_Gr_2	1	0.99034	0.35274	7.8822	0.0050	2.692	1.348	5.375
Triglycerides_Ls_150	1	-0.56033	0.22953	5.9594	0.0146	0.571	0.364	0.895
HDL_Ls_40_M_Ls_50_F	1	0.15770	0.21972	0.5151	0.4729	1.171	0.761	1.801
Glucose_Gr_110	1	0.75243	0.20701	13.2114	0.0003	2.122	1.414	3.184

5-Year AMI Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	AMI5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	107	4077	97.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1755.888	1676.181
AIC	1755.888	1696.181
SBC	1755.888	1722.910

5-Year AMI Mortality Cox proportional Hazards Regression Model w/blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	79.7063	10	<.0001
Score	85.9212	10	<.0001
Wald	79.4891	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	-0.26375	0.21562	1.4964	0.2212	0.768	0.503	1.172
BUN_Gr_40_OR_Creat_Gr_2	1	0.67327	0.35841	3.5287	0.0603	1.961	0.971	3.958
Triglycerides_Ls_150	1	-0.52683	0.22886	5.2989	0.0213	0.590	0.377	0.925
HDL_Ls_40_M_Ls_50_F	1	0.27265	0.21929	1.5459	0.2137	1.313	0.855	2.019
Glucose_Gr_110	1	0.72403	0.20713	12.2182	0.0005	2.063	1.374	3.096
Female	1	-1.17961	0.22181	28.2826	<.0001	0.307	0.199	0.475
age_6	1	0.06032	0.01681	12.8764	0.0003	1.062	1.028	1.098
White	1	0.18919	0.21218	0.7951	0.3726	1.208	0.797	1.831
Married	1	-0.11299	0.21869	0.2670	0.6054	0.893	0.582	1.371
Edu_Ls_7_year	1	0.27123	0.24839	1.1924	0.2749	1.312	0.806	2.134

5-Year AMI Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	AMI5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	107	4077	97.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1755.888	1613.378
AIC	1755.888	1679.378
SBC	1755.888	1767.581

5-Year AMI Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	142.5101	33	<.0001
Score	156.9387	33	<.0001
Wald	142.8223	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Confidence	Ratio Limits
LDL_Ls_200	1	-0.38116	0.21966	3.0109	0.0827	0.683	0.444	1.051
BUN_Gr_40_OR_Creat_Gr_2	1	0.29402	0.37024	0.6306	0.4271	1.342	0.649	2.772
Triglycerides_Ls_150	1	-0.45826	0.23313	3.8640	0.0493	0.632	0.400	0.999
HDL_Ls_40_M_Ls_50_F	1	0.08859	0.22766	0.1514	0.6972	1.093	0.699	1.707
Glucose_Gr_110	1	0.61348	0.21347	8.2589	0.0041	1.847	1.215	2.806
Female	1	-1.36701	0.24123	32.1124	<.0001	0.255	0.159	0.409
age_6	1	0.03336	0.01819	3.3627	0.0667	1.034	0.998	1.071
White	1	0.24346	0.22987	1.1217	0.2896	1.276	0.813	2.002
Married	1	-0.05046	0.22095	0.0522	0.8193	0.951	0.617	1.466
Edu_Ls_7_year	1	0.30626	0.25307	1.4646	0.2262	1.358	0.827	2.231
DM_score	1	0.10041	0.05318	3.5653	0.0590	1.106	0.996	1.227
Canx_score	1	-0.15581	0.11236	1.9231	0.1655	0.856	0.687	1.067
HxAMI_score	1	0.06329	0.07289	0.7540	0.3852	1.065	0.924	1.229
DM_suspect_score	1	-0.83785	0.89361	0.8791	0.3485	0.433	0.075	2.493
Hx_Cu_Smoker_score	1	0.16723	0.05950	7.8999	0.0049	1.182	1.052	1.328
HTN_score	1	-0.03717	0.06097	0.3717	0.5421	0.964	0.855	1.086

Obesity_score	1	-0.02631	0.04081	0.4156	0.5191	0.974	0.899	1.055
BP_Med	1	0.15727	0.21490	0.5356	0.4643	1.170	0.768	1.783
ChxPain	1	0.71790	0.43675	2.7019	0.1002	2.050	0.871	4.826
BP_S_Gr_160	1	0.19139	0.31361	0.3724	0.5417	1.211	0.655	2.239
BP_D_Ls_90	1	-0.46577	0.25028	3.4635	0.0627	0.628	0.384	1.025
pulse_10	1	0.06958	0.07645	0.8285	0.3627	1.072	0.923	1.245
ETOH_use	1	-0.10842	0.21203	0.2614	0.6091	0.897	0.592	1.360
ADLscorebase	1	-9.74559	519.14622	0.0004	0.9850	0.000	0.000	
GrossMobilityBase	1	-0.05434	0.12987	0.1751	0.6756	0.947	0.734	1.222
PPDscorebase	1	0.13681	0.14102	0.9412	0.3320	1.147	0.870	1.512
SPMSQscorebase	1	-0.04864	0.08329	0.3410	0.5592	0.953	0.809	1.121
BP_S_Gr_160_6	1	-0.55703	0.39732	1.9655	0.1609	0.573	0.263	1.248
BP_D_Ls_90_6	1	-0.56231	0.28271	3.9562	0.0467	0.570	0.327	0.992
pulse_10_6	1	0.18052	0.07601	5.6406	0.0175	1.198	1.032	1.390
ADLscorebase_6	1	-0.40808	0.68828	0.3515	0.5533	0.665	0.173	2.562
GrossMobilityBase_6	1	-0.31718	0.10694	8.7967	0.0030	0.728	0.591	0.898
PPDscorebase_6	1	-0.09209	0.12426	0.5492	0.4587	0.912	0.715	1.164

5-year CAD Mortality Cox proportional Hazards Regression Model

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	CAD5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	149	4035	96.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2444.961	2411.221
AIC	2444.961	2421.221
SBC	2444.961	2436.241

5-year CAD Mortality Cox proportional Hazards Regression Model w/ Blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	33.7406	5	<.0001
Score	39.7659	5	<.0001
Wald	37.6758	5	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.40909	0.17256	5.6201	0.0178	1.505	1.073	2.111
BUN_Gr_40_OR_Creat_Gr_2	1	0.96839	0.30539	10.0551	0.0015	2.634	1.447	4.792
Triglycerides_Ls_150	1	0.31480	0.18300	2.9591	0.0854	1.370	0.957	1.961
HDL_Ls_40_M_Ls_50_F	1	0.39384	0.18507	4.5288	0.0333	1.483	1.032	2.131
Glucose_Gr_110	1	0.42185	0.16837	6.2775	0.0122	1.525	1.096	2.121

5-year CAD Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	CAD5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	149	4035	96.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2444.961	2349.452
AIC	2444.961	2369.452
SBC	2444.961	2399.491

5-year CAD Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	95.5096	10	<.0001
Score	116.5917	10	<.0001
Wald	111.8582	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.18039	0.18069	0.9967	0.3181	1.198	0.841	1.707
BUN_Gr_40_OR_Creat_Gr_2	1	0.65393	0.31318	4.3599	0.0368	1.923	1.041	3.553
Triglycerides_Ls_150	1	0.25066	0.18393	1.8572	0.1730	1.285	0.896	1.843
HDL_Ls_40_M_Ls_50_F	1	0.44489	0.18542	5.7568	0.0164	1.560	1.085	2.244
Glucose_Gr_110	1	0.40056	0.16890	5.6242	0.0177	1.493	1.072	2.078
Female	1	-0.32472	0.18979	2.9272	0.0871	0.723	0.498	1.048
age_6	1	0.09683	0.01318	53.9589	<.0001	1.102	1.074	1.131
White	1	0.28349	0.18630	2.3156	0.1281	1.328	0.922	1.913
Married	1	-0.03510	0.18697	0.0352	0.8511	0.966	0.669	1.393
Edu_Ls_7_year	1	0.00876	0.22644	0.0015	0.9691	1.009	0.647	1.572

5-year CAD Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	CAD5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	149	4035	96.44

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2444.961	2270.678
AIC	2444.961	2336.678
SBC	2444.961	2435.808

5-year CAD Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	174.2834	33	<.0001
Score	237.0109	33	<.0001
Wald	197.1807	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.16848	0.18367	0.8414	0.3590	1.184	0.826	1.696
BUN_Gr_40_OR_Creat_Gr_2	1	0.44046	0.31868	1.9103	0.1669	1.553	0.832	2.901
Triglycerides_Ls_150	1	0.29833	0.18810	2.5153	0.1127	1.348	0.932	1.948
HDL_Ls_40_M_Ls_50_F	1	0.28190	0.18949	2.2132	0.1368	1.326	0.914	1.922
Glucose_Gr_110	1	0.25102	0.17528	2.0509	0.1521	1.285	0.912	1.812
Female	1	-0.60233	0.20771	8.4095	0.0037	0.548	0.364	0.823
age_6	1	0.06650	0.01493	19.8528	<.0001	1.069	1.038	1.100
White	1	0.34194	0.19891	2.9551	0.0856	1.408	0.953	2.079
Married	1	-0.03257	0.19114	0.0290	0.8647	0.968	0.666	1.408
Edu_Ls_7_year	1	-0.0009597	0.23039	0.0000	0.9967	0.999	0.636	1.569
DM_score	1	0.09210	0.04894	3.5418	0.0598	1.096	0.996	1.207
Canx_score	1	-0.00208	0.06719	0.0010	0.9753	0.998	0.875	1.138
HxAMI_score	1	0.19047	0.04845	15.4568	<.0001	1.210	1.100	1.330
DM_suspect_score	1	0.05444	0.11358	0.2298	0.6317	1.056	0.845	1.319

Hx_Cu_Smoker_score	1	-0.00736	0.07955	0.0086	0.9263	0.993	0.849	1.160
HTN_score	1	-0.04545	0.05327	0.7279	0.3936	0.956	0.861	1.061
Obesity_score	1	0.01401	0.03363	0.1735	0.6770	1.014	0.949	1.083
BP_Med	1	0.41116	0.17682	5.4069	0.0201	1.509	1.067	2.133
ChxPain	1	0.65447	0.37787	2.9998	0.0833	1.924	0.917	4.035
BP_S_Gr_160	1	0.28009	0.27187	1.0613	0.3029	1.323	0.777	2.255
BP_D_Ls_90	1	0.29328	0.25166	1.3581	0.2439	1.341	0.819	2.196
pulse_10	1	0.03437	0.06314	0.2963	0.5862	1.035	0.914	1.171
ETOH_use	1	-0.16201	0.18553	0.7625	0.3825	0.850	0.591	1.223
ADLscorebase	1	0.16116	0.26077	0.3819	0.5366	1.175	0.705	1.959
GrossMobilityBase	1	-0.09155	0.10794	0.7193	0.3964	0.913	0.739	1.128
PPDscorebase	1	-0.10821	0.11911	0.8254	0.3636	0.897	0.711	1.133
SPMSQscorebase	1	-0.03426	0.06657	0.2649	0.6068	0.966	0.848	1.101
BP_S_Gr_160_6	1	0.52484	0.30577	2.9462	0.0861	1.690	0.928	3.078
BP_D_Ls_90_6	1	-0.21062	0.25511	0.6816	0.4090	0.810	0.491	1.336
pulse_10_6	1	0.0003047	0.06299	0.0000	0.9961	1.000	0.884	1.132
ADLscorebase_6	1	0.40059	0.15896	6.3509	0.0117	1.493	1.093	2.038
GrossMobilityBase_6	1	-0.36493	0.09068	16.1975	<.0001	0.694	0.581	0.829
PPDscorebase_6	1	-0.03778	0.09907	0.1455	0.7029	0.963	0.793	1.169

5-year Stroke Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Stroke5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	90	4094	97.85

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1474.393	1462.836
AIC	1474.393	1472.836
SBC	1474.393	1485.335

5-year Stroke Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	11.5563	5	0.0414
Score	16.6998	5	0.0051
Wald	14.9155	5	0.0107

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.19782	0.22660	0.7621	0.3827	1.219	0.782	1.900
BUN_Gr_40_OR_Creat_Gr_2	1	1.27034	0.37565	11.4359	0.0007	3.562	1.706	7.438
Triglycerides_Ls_150	1	-0.35474	0.23884	2.2060	0.1375	0.701	0.439	1.120
HDL_Ls_40_M_Ls_50_F	1	-0.22038	0.23346	0.8911	0.3452	0.802	0.508	1.268
Glucose_Gr_110	1	0.09835	0.21567	0.2080	0.6484	1.103	0.723	1.684

5-year Stroke Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Stroke5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	90	4094	97.85

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1474.393	1432.814
AIC	1474.393	1452.814
SBC	1474.393	1477.813

5-year Stroke Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	41.5781	10	<.0001
Score	51.1271	10	<.0001
Wald	48.5744	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.00729	0.23708	0.0009	0.9755	1.007	0.633	1.603
BUN_Gr_40_OR_Creat_Gr_2	1	1.05740	0.38409	7.5788	0.0059	2.879	1.356	6.112
Triglycerides_Ls_150	1	-0.38818	0.23981	2.6202	0.1055	0.678	0.424	1.085
HDL_Ls_40_M_Ls_50_F	1	-0.19601	0.23464	0.6978	0.4035	0.822	0.519	1.302
Glucose_Gr_110	1	0.08755	0.21684	0.1630	0.6864	1.091	0.714	1.670
Female	1	-0.14078	0.24479	0.3307	0.5652	0.869	0.538	1.404
age_6	1	0.08317	0.01754	22.4735	<.0001	1.087	1.050	1.125
White	1	0.32736	0.23963	1.8663	0.1719	1.387	0.867	2.219
Married	1	0.13472	0.23813	0.3201	0.5716	1.144	0.717	1.825
Edu_Ls_7_year	1	0.56861	0.25703	4.8940	0.0270	1.766	1.067	2.922

5-year Stroke Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Stroke5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	90	4094	97.85

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1474.393	1362.300
AIC	1474.393	1428.300
SBC	1474.393	1510.793

5-year Stroke Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	112.0930	33	<.0001
Score	151.1676	33	<.0001
Wald	121.7908	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	-0.04051	0.24159	0.0281	0.8668	0.960	0.598	1.542
BUN_Gr_40_OR_Creat_Gr_2	1	0.70195	0.38905	3.2554	0.0712	2.018	0.941	4.325
Triglycerides_Ls_150	1	-0.30866	0.24398	1.6004	0.2058	0.734	0.455	1.185
HDL_Ls_40_M_Ls_50_F	1	-0.30407	0.23929	1.6147	0.2038	0.738	0.462	1.179
Glucose_Gr_110	1	-0.00278	0.22459	0.0002	0.9901	0.997	0.642	1.549
Female	1	-0.57900	0.27131	4.5544	0.0328	0.560	0.329	0.954
age_6	1	0.04600	0.01965	5.4781	0.0193	1.047	1.008	1.088
White	1	0.33584	0.25785	1.6964	0.1928	1.399	0.844	2.319
Married	1	0.21872	0.24118	0.8224	0.3645	1.244	0.776	1.997
Edu_Ls_7_year	1	0.55008	0.26555	4.2908	0.0383	1.733	1.030	2.917
DM_score	1	-0.04501	0.09117	0.2438	0.6215	0.956	0.800	1.143
Canx_score	1	-0.19482	0.14013	1.9327	0.1645	0.823	0.625	1.083
HxAMI_score	1	0.12889	0.07886	2.6716	0.1022	1.138	0.975	1.328

DM_suspect_score	1	-12.64392	473.12529	0.0007	0.9787	0.000	0.000	
Hx_Cu_Smoker_score	1	-0.24266	0.16387	2.1929	0.1387	0.785	0.569	1.082
HTN_score	1	0.05471	0.05713	0.9169	0.3383	1.056	0.944	1.181
Obesity_score	1	-0.04530	0.04728	0.9179	0.3380	0.956	0.871	1.049
BP_Med	1	0.35940	0.22726	2.5009	0.1138	1.432	0.918	2.236
ChxPain	1	0.56644	0.52296	1.1732	0.2787	1.762	0.632	4.911
BP_S_Gr_160	1	-0.02762	0.34852	0.0063	0.9368	0.973	0.491	1.926
BP_D_Ls_90	1	-0.34230	0.28431	1.4495	0.2286	0.710	0.407	1.240
pulse_10	1	0.12691	0.07736	2.6911	0.1009	1.135	0.976	1.32
ETOH_use	1	-0.19856	0.23997	0.6846	0.4080	0.820	0.512	1.312
ADLscorebase	1	-11.80416	1254	0.0001	0.9925	0.000	0.000	
GrossMobilityBase	1	-0.35566	0.13173	7.2891	0.0069	0.701	0.541	0.907
PPDscorebase	1	0.15184	0.13572	1.2516	0.2632	1.164	0.892	1.519
SPMSQscorebase	1	-0.12029	0.08951	1.8061	0.1790	0.887	0.744	1.057
BP_S_Gr_160_6	1	0.01607	0.39141	0.0017	0.9673	1.016	0.472	2.188
BP_D_Ls_90_6	1	-0.10032	0.32388	0.0959	0.7568	0.905	0.479	1.707
pulse_10_6	1	0.08489	0.07883	1.1595	0.2816	1.089	0.933	1.270
ADLscorebase_6	1	0.44139	0.17349	6.4728	0.0110	1.555	1.107	2.185
GrossMobilityBase_6	1	-0.20533	0.12080	2.8890	0.0892	0.814	0.643	1.032
PPDscorebase_6	1	-0.11843	0.13381	0.7833	0.3761	0.888	0.683	1.155

5-year HF Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	HF5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	80	4104	98.09

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1310.413	1255.775
AIC	1310.413	1265.775
SBC	1310.413	1277.685

5-year HF Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	54.6388	5	<.0001
Score	109.7353	5	<.0001
Wald	77.5399	5	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	-0.17920	0.24321	0.5429	0.4612	0.836	0.519	1.346
BUN_Gr_40_OR_Creat_Gr_2	1	2.11027	0.28937	53.1823	<.0001	8.251	4.679	14.548
Triglycerides_Ls_150	1	0.40950	0.24957	2.6923	0.1008	1.506	0.923	2.456
HDL_Ls_40_M_Ls_50_F	1	0.28927	0.25639	1.2730	0.2592	1.335	0.808	2.207
Glucose_Gr_110	1	0.80196	0.24051	11.1182	0.0009	2.230	1.392	3.573

5-year HF Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	HF5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	80	4104	98.09

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1310.413	1205.594
AIC	1310.413	1225.594
SBC	1310.413	1249.414

5-year HF Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	104.8192	10	<.0001
Score	171.5610	10	<.0001
Wald	136.9073	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	-0.54926	0.25972	4.4725	0.0344	0.577	0.347	0.961
BUN_Gr_40_OR_Creat_Gr_2	1	1.74272	0.30472	32.7079	<.0001	5.713	3.144	10.381
Triglycerides_Ls_150	1	0.26953	0.25164	1.1473	0.2841	1.309	0.800	2.144
HDL_Ls_40_M_Ls_50_F	1	0.31877	0.25760	1.5313	0.2159	1.375	0.830	2.279
Glucose_Gr_110	1	0.70870	0.24225	8.5585	0.0034	2.031	1.264	3.266
Female	1	-0.83482	0.25676	10.5710	0.0011	0.434	0.262	0.718
age_6	1	0.10909	0.01814	36.1513	<.0001	1.115	1.076	1.156
White	1	0.09843	0.24542	0.1609	0.6884	1.103	0.682	1.785
Married	1	-0.51198	0.25755	3.9518	0.0468	0.599	0.362	0.993
Edu_Ls_7_year	1	-0.07325	0.30534	0.0576	0.8104	0.929	0.511	1.691

5-year HF Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	HF5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	80	4104	98.09

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1310.413	1146.297
AIC	1310.413	1212.297
SBC	1310.413	1290.904

5-year HF Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	164.1162	33	<.0001
Score	243.9352	33	<.0001
Wald	188.5526	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	-0.62722	0.26917	5.4296	0.0198	0.534	0.315	0.905
BUN_Gr_40_OR_Creat_Gr_2	1	1.50097	0.31886	22.1581	<.0001	4.486	2.401	8.381
Triglycerides_Ls_150	1	0.29983	0.26206	1.3090	0.2526	1.350	0.808	2.256
HDL_Ls_40_M_Ls_50_F	1	0.06592	0.26801	0.0605	0.8057	1.068	0.632	1.806
Glucose_Gr_110	1	0.48818	0.25227	3.7449	0.0530	1.629	0.994	2.671
Female	1	-1.20076	0.28572	17.6620	<.0001	0.301	0.172	0.527
age_6	1	0.07373	0.02021	13.3072	0.0003	1.077	1.035	1.120
White	1	0.21203	0.27198	0.6078	0.4356	1.236	0.725	2.107
Married	1	-0.49548	0.26497	3.4969	0.0615	0.609	0.362	1.024
Edu_Ls_7_year	1	-0.18520	0.31927	0.3365	0.5619	0.831	0.444	1.554
DM_score	1	0.20410	0.05598	13.2926	0.0003	1.226	1.099	1.369
Canx_score	1	0.00820	0.09248	0.0079	0.9294	1.008	0.841	1.209
HxAMI_score	1	0.19985	0.06715	8.8573	0.0029	1.221	1.071	1.393
DM_suspect_score	1	0.02778	0.16851	0.0272	0.8690	1.028	0.739	1.431

Hx_Cu_Smoker_score	1	0.04542	0.10153	0.2001	0.6546	1.046	0.858	1.277
HTN_score	1	-0.08493	0.08195	1.0741	0.3000	0.919	0.782	1.079
Obesity_score	1	-0.00461	0.04713	0.0096	0.9221	0.995	0.908	1.092
BP_Med	1	-0.03263	0.25724	0.0161	0.8991	0.968	0.585	1.602
ChxPain	1	0.49426	0.54439	0.8243	0.3639	1.639	0.564	4.765
BP_S_Gr_160	1	-0.29616	0.37541	0.6223	0.4302	0.744	0.356	1.552
BP_D_Ls_90	1	-0.10933	0.32373	0.1141	0.7356	0.896	0.475	1.691
pulse_10	1	0.17293	0.08815	3.8481	0.0498	1.189	1.000	1.413
ETOH_use	1	-0.45790	0.27084	2.8583	0.0909	0.633	0.372	1.076
ADLscorebase	1	-9.16952	510.26784	0.0003	0.9857	0.000	0.000	
GrossMobilityBase	1	-0.05328	0.14383	0.1372	0.7111	0.948	0.715	1.257
PPDscorebase	1	-0.00405	0.15911	0.0006	0.9797	0.996	0.729	1.360
SPMSQscorebase	1	0.00600	0.09023	0.0044	0.9470	1.006	0.843	1.201
BP_S_Gr_160_6	1	0.57719	0.40113	2.0705	0.1502	1.781	0.811	3.909
BP_D_Ls_90_6	1	0.36016	0.42591	0.7151	0.3978	1.434	0.622	3.303
pulse_10_6	1	0.04230	0.08390	0.2542	0.6141	1.043	0.885	1.230
ADLscorebase_6	1	0.09560	0.39520	0.0585	0.8089	1.100	0.507	2.387
GrossMobilityBase_6	1	-0.41218	0.12844	10.2985	0.0013	0.662	0.515	0.852
PPDscorebase_6	1	0.02232	0.13541	0.0272	0.8691	1.023	0.784	1.333

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Other5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	536	3648	87.19

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	8798.711	8694.421
AIC	8798.711	8704.421
SBC	8798.711	8725.842

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	104.2892	5	<.0001
Score	127.0367	5	<.0001
Wald	119.0430	5	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.52871	0.09112	33.6666	<.0001	1.697	1.419	2.029
BUN_Gr_40_OR_Creat_Gr_2	1	1.10849	0.15981	48.1103	<.0001	3.030	2.215	4.144
Triglycerides_Ls_150	1	0.29612	0.09791	9.1472	0.0025	1.345	1.110	1.629
HDL_Ls_40_M_Ls_50_F	1	-0.04685	0.09560	0.2402	0.6241	0.954	0.791	1.151
Glucose_Gr_110	1	0.23751	0.08826	7.2423	0.0071	1.268	1.067	1.508

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Other5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	536	3648	87.19

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	8798.711	8590.815
AIC	8798.711	8610.815
SBC	8798.711	8653.657

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	207.8954	10	<.0001
Score	244.1674	10	<.0001
Wald	235.5889	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.31839	0.09490	11.2567	0.0008	1.375	1.142	1.656
BUN_Gr_40_OR_Creat_Gr_2	1	0.86619	0.16339	28.1043	<.0001	2.378	1.726	3.275
Triglycerides_Ls_150	1	0.29410	0.09818	8.9728	0.0027	1.342	1.107	1.627
HDL_Ls_40_M_Ls_50_F	1	0.00744	0.09588	0.0060	0.9381	1.007	0.835	1.216
Glucose_Gr_110	1	0.20293	0.08844	5.2648	0.0218	1.225	1.030	1.457
Female	1	-0.64206	0.09761	43.2710	<.0001	0.526	0.435	0.637
age_6	1	0.05309	0.00730	52.8282	<.0001	1.055	1.040	1.070
White	1	0.07952	0.09412	0.7138	0.3982	1.083	0.900	1.302
Married	1	-0.29503	0.09717	9.2199	0.0024	0.745	0.615	0.901
Edu_Ls_7_year	1	0.19363	0.11285	2.9438	0.0862	1.214	0.973	1.514

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	Other5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	536	3648	87.19

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	8798.711	8439.145
AIC	8798.711	8505.145
SBC	8798.711	8646.522

5-year Other Deaths Cox proportional Hazards Regression Model w/ blood all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	359.5651	33	<.0001
Score	426.5801	33	<.0001
Wald	393.3818	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.22600	0.09618	5.5218	0.0188	1.254	1.038	1.514
BUN_Gr_40_OR_Creat_Gr_2	1	0.67800	0.16795	16.2967	<.0001	1.970	1.417	2.738
Triglycerides_Ls_150	1	0.32747	0.09946	10.8396	0.0010	1.387	1.142	1.686
HDL_Ls_40_M_Ls_50_F	1	-0.02809	0.09720	0.0835	0.7726	0.972	0.804	1.176
Glucose_Gr_110	1	0.12974	0.09104	2.0308	0.1541	1.139	0.952	1.361
Female	1	-0.75188	0.10524	51.0417	<.0001	0.471	0.384	0.579
age_6	1	0.02471	0.00799	9.5612	0.0020	1.025	1.009	1.041
White	1	0.10766	0.09917	1.1785	0.2777	1.114	0.917	1.353
Married	1	-0.22809	0.09806	5.4110	0.0200	0.796	0.657	0.965
Edu_Ls_7_year	1	0.15421	0.11532	1.7883	0.1811	1.167	0.931	1.463
DM_score	1	0.03536	0.02996	1.3932	0.2379	1.036	0.977	1.099
Canx_score	1	0.07636	0.02907	6.9011	0.0086	1.079	1.020	1.143
HxAMI_score	1	0.01191	0.04041	0.0869	0.7682	1.012	0.935	1.095
DM_suspect_score	1	0.02919	0.06674	0.1913	0.6618	1.030	0.903	1.174

Hx_Cu_Smoker_score	1	0.09190	0.03191	8.2927	0.0040	1.096	1.030	1.167
HTN_score	1	-0.04036	0.02778	2.1109	0.1463	0.960	0.910	1.014
Obesity_score	1	-0.01488	0.01887	0.6219	0.4304	0.985	0.949	1.022
BP_Med	1	0.01424	0.09824	0.0210	0.8848	1.014	0.837	1.230
ChxPain	1	-0.11925	0.28504	0.1750	0.6757	0.888	0.508	1.552
BP_S_Gr_160	1	-0.22939	0.15341	2.2358	0.1348	0.795	0.589	1.074
BP_D_Ls_90	1	-0.08947	0.12080	0.5486	0.4589	0.914	0.722	1.159
pulse_10	1	0.08814	0.03339	6.9684	0.0083	1.092	1.023	1.166
ETOH_use	1	0.09252	0.09349	0.9793	0.3224	1.097	0.913	1.318
ADLscorebase	1	0.15747	0.17537	0.8063	0.3692	1.171	0.830	1.651
GrossMobilityBase	1	-0.03070	0.05902	0.2705	0.6030	0.970	0.864	1.089
PPDscorebase	1	-0.08941	0.06730	1.7651	0.1840	0.914	0.801	1.043
SPMSQscorebase	1	0.00493	0.03466	0.0203	0.8868	1.005	0.939	1.076
BP_S_Gr_160_6	1	0.07361	0.18452	0.1591	0.6899	1.076	0.750	1.545
BP_D_Ls_90_6	1	-0.36711	0.13294	7.6253	0.0058	0.693	0.534	0.899
pulse_10_6	1	-0.03436	0.03312	1.0763	0.2995	0.966	0.905	1.031
ADLscorebase_6	1	0.21535	0.11543	3.4803	0.0621	1.240	0.989	1.555
GrossMobilityBase_6	1	-0.39061	0.04727	68.2699	<.0001	0.677	0.617	0.742
PPDscorebase_6	1	0.10191	0.04997	4.1592	0.0414	1.107	1.004	1.221

5-year All Cause Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	obs5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	1043	3141	75.07

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	17110.887	16912.111
AIC	17110.887	16922.111
SBC	17110.887	16946.860

5-year All Cause Mortality Cox proportional Hazards Regression Model w/ blood

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	198.7761	5	<.0001
Score	269.8251	5	<.0001
Wald	244.9357	5	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.41126	0.06529	39.6705	<.0001	1.509	1.327	1.715
BUN_Gr_40_OR_Creat_Gr_2	1	1.22705	0.10791	129.2953	<.0001	3.411	2.761	4.215
Triglycerides_Ls_150	1	0.15556	0.06945	5.0164	0.0251	1.168	1.020	1.339
HDL_Ls_40_M_Ls_50_F	1	0.05651	0.06898	0.6713	0.4126	1.058	0.924	1.211
Glucose_Gr_110	1	0.34139	0.06346	28.9405	<.0001	1.407	1.242	1.593

5-year All Cause Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	obs5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	1043	3141	75.07

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	17110.887	16614.298
AIC	17110.887	16634.298
SBC	17110.887	16683.796

5-year All Cause Mortality Cox proportional Hazards Regression Model w/ blood + demo

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	496.5896	10	<.0001
Score	616.3185	10	<.0001
Wald	587.2379	10	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.15828	0.06825	5.3790	0.0204	1.171	1.025	1.339
BUN_Gr_40_OR_Creat_Gr_2	1	0.92866	0.11073	70.3420	<.0001	2.531	2.037	3.145
Triglycerides_Ls_150	1	0.13220	0.06961	3.6068	0.0575	1.141	0.996	1.308
HDL_Ls_40_M_Ls_50_F	1	0.11536	0.06911	2.7860	0.0951	1.122	0.980	1.285
Glucose_Gr_110	1	0.30250	0.06363	22.5990	<.0001	1.353	1.195	1.533
Female	1	-0.65263	0.07035	86.0567	<.0001	0.521	0.454	0.598
age_6	1	0.07364	0.00513	206.3928	<.0001	1.076	1.066	1.087
White	1	0.10032	0.06786	2.1858	0.1393	1.106	0.968	1.263
Married	1	-0.20715	0.07000	8.7567	0.0031	0.813	0.709	0.932
Edu_Ls_7_year	1	0.17150	0.08097	4.4863	0.0342	1.187	1.013	1.391

5-year All Cause Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Model Information

Data Set	WORK.EPESE_6_3
Dependent Variable	day5y_6
Censoring Variable	obs5y_6
Censoring Value(s)	0
Ties Handling	BRESLOW

Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
4184	1043	3141	75.07

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	17110.887	16308.145
AIC	17110.887	16374.145
SBC	17110.887	16537.491

5-year All Cause Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	802.7419	33	<.0001
Score	979.7613	33	<.0001
Wald	878.6071	33	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LDL_Ls_200	1	0.07791	0.06923	1.2663	0.2605	1.081	0.944	1.238
BUN_Gr_40_OR_Creat_Gr_2	1	0.71070	0.11342	39.2662	<.0001	2.035	1.630	2.542
Triglycerides_Ls_150	1	0.16963	0.07085	5.7323	0.0167	1.185	1.031	1.361
HDL_Ls_40_M_Ls_50_F	1	0.02764	0.07035	0.1543	0.6944	1.028	0.896	1.180
Glucose_Gr_110	1	0.20132	0.06554	9.4367	0.0021	1.223	1.076	1.391
Female	1	-0.83833	0.07632	120.6452	<.0001	0.432	0.372	0.502
age_6	1	0.04275	0.00563	57.7126	<.0001	1.044	1.032	1.055
White	1	0.12971	0.07218	3.2300	0.0723	1.139	0.988	1.312
Married	1	-0.14881	0.07075	4.4243	0.0354	0.862	0.750	0.990
Edu_Ls_7_year	1	0.13362	0.08252	2.6220	0.1054	1.143	0.972	1.344
DM_score	1	0.06280	0.01977	10.0881	0.0015	1.065	1.024	1.107
Canx_score	1	0.02548	0.02341	1.1845	0.2764	1.026	0.980	1.074
HxAMI_score	1	0.07650	0.02411	10.0677	0.0015	1.080	1.030	1.132

DM_suspect_score	1	-0.00602	0.05191	0.0135	0.9077	0.994	0.898	1.100
Hx_Cu_Smoker_score	1	0.06678	0.02450	7.4287	0.0064	1.069	1.019	1.122
HTN_score	1	-0.02331	0.01951	1.4279	0.2321	0.977	0.940	1.015
Obesity_score	1	-0.02065	0.01351	2.3366	0.1264	0.980	0.954	1.006
BP_Med	1	0.07892	0.06927	1.2979	0.2546	1.082	0.945	1.239
ChxPain	1	0.32759	0.16677	3.8584	0.0495	1.388	1.001	1.924
BP_S_Gr_160	1	-0.07653	0.10576	0.5236	0.4693	0.926	0.753	1.140
BP_D_Ls_90	1	-0.07086	0.08642	0.6722	0.4123	0.932	0.786	1.104
pulse_10	1	0.08040	0.02401	11.2132	0.0008	1.084	1.034	1.136
ETOH_use	1	-0.04945	0.06807	0.5277	0.4676	0.952	0.833	1.088
ADLscorebase	1	0.03499	0.13892	0.0634	0.8011	1.036	0.789	1.360
GrossMobilityBase	1	-0.07355	0.04106	3.2089	0.0732	0.929	0.857	1.007
PPDscorebase	1	-0.04041	0.04573	0.7811	0.3768	0.960	0.878	1.050
SPMSQscorebase	1	-0.01638	0.02482	0.4356	0.5092	0.984	0.937	1.033
BP_S_Gr_160_6	1	0.10205	0.12438	0.6732	0.4119	1.107	0.868	1.413
BP_D_Ls_90_6	1	-0.27449	0.09490	8.3665	0.0038	0.760	0.631	0.915
pulse_10_6	1	0.02011	0.02369	0.7200	0.3961	1.020	0.974	1.069
ADLscorebase_6	1	0.25957	0.07567	11.7665	0.0006	1.296	1.118	1.504
GrossMobilityBase_6	1	-0.37924	0.03407	123.8925	<.0001	0.684	0.640	0.732
PPDscorebase_6	1	0.01990	0.03701	0.2891	0.5908	1.020	0.949	1.097

5-year All Cause Mortality Cox proportional Hazards Regression Model all together

The PHREG Procedure

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APPENDIX 5: HIC Exemption from Review

Yale University
Human Investigation Committee
School of Medicine
47 College Street, Suite 204 Telephone: 203/785-4688
New Haven, Connecticut 06520-8010 Fax: 203/785-2847

REQUEST FOR EXEMPTION FROM COMMITTEE REVIEW

Title of Project: Examination of the Prognostic Value of HDL-C Levels on Cardiovascular Morbidity, Mortality, and Overall Health Status in an Elderly Population

Principal Investigator: Lisa M. Millman

Dept: Yale School of Medicine—Dept of Internal Medicine, Cardiology Section

PI's Association or Status with Yale: Yale Medical Student

Other Investigator(s):
JoAnne M. Foody, MD—Dept of Internal Medicine, Cardiology Section

Certain research activities may be exempt from review, if approved by the HIC Chair or his/her designee and confirmed in writing to the Investigator. Research may be exempt from review when the only involvement of human subjects in the research falls into one of the categories noted below.

- 45 CFR 46.101(b)(4)Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. "***Existing" is the keyword here. It means that all the data, documents, etc. must be "on the shelf" when the study is started and no additional data, etc. may be added to the set of data.***

1) ***Describe the purpose of the study***
2) ***Describe how data will be recorded so that subjects will not be identified***
3) ***Describe the procedures that will be used.***

Statement of Hypothesis and Specific Aims

Morbidity and mortality from cardiovascular disease is a major health problem in the United States with elderly adults (>65 years) experiencing the greatest number of coronary heart disease related events and deaths [1]. Older adults shoulder the highest risks associated with cardiovascular disease and stand the most chance to benefit if predictors of risk can be stratified within the this population and appropriate interventions put into place. Serum cholesterol and high-density lipoprotein (HDL-C) levels seem to be a good place to start given their strong prognostic value in a middle-aged population [2-4], but their value in an elderly population is controversial with conflicting data [3-6].

This study proposal seeks to build upon previous studies in an elderly population using data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE), which provides a rich source of longitudinal clinical, functional, and social information on individuals >65 years old. Over 5,000 of these participants had a blood draw at the 6th annual follow-up providing serum cholesterol, HDL-C, and triglycerides, as well as additional biochemical variables. Since the study has been closed at all sites since 1992, it is now possible to review complete 10 year mortality data in this well-studied

population. This proposal has the following aims utilizing this data available from the EPESE project:

AIM 1: To determine if HDL-C levels and HDL-C to total serum cholesterol ratios are prognostic for cardiovascular morbidity and mortality in the entire EPESE population with serum samples

AIM 2: To evaluate the degree to which HDL-C levels and HDL-C to total serum cholesterol ratios are associated with outcomes in those with prior cardiovascular history (recurrence) vs. those without prior history (new events)

AIM 3: To determine if HDL-C levels and HDL-C to total serum cholesterol ratios correlate with other outcome measures of overall health status including number of chronic conditions, depressive symptoms, cognitive and physical functioning

Research Design and Methods

Data Collection

Studies of the Elderly (EPESE), initiated in 1980 by the Epidemiology, Demography, and Biometry Program (EDBP) at the National Institutes of Aging to study health, social, psychological, and economic aspects of the elderly. EPESE incorporates cross-sectional data and This project will use data from the Established Populations for

Epidemiologic continued surveillance beginning in 1981 with annual follow-up of more than 10,000 subjects age 65 and older. Study participants were recruited from 3 communities: East Boston, MA, Iowa and Washington Counties, Iowa; and New Haven, CT between 1981 and 1982 with an additional 4th site in the Piedmont area of North Carolina added in 1986. In East Boston and the Iowa counties, the study samples represented the total populations 65 years of age and older; in New Haven, the sample derived from a stratified (by housing type and sex) random sample of residents. Between 80 and 84% of eligible persons in the three communities participated. Participants were followed from 1981 to 1988 with annual in-person (1982, 1985, 1988) and telephone interviews (1989 and 1990/91). During the in-person interviews (which were done at baseline and at the 3rd and 6th follow-up points), participants were asked about their health habits, functional status, chronic conditions, and hospitalization history and had their blood pressure measured at home.

Important to this proposal, in 1987-88, (sixth annual follow-up) blood samples were obtained from 65% of the 6,566 surviving participants greater than or equal to 71 years of age providing 4,128 useful measures for total cholesterol, HDL-C, glucose, Hgb A1c and albumin.

Participants were non-fasting at the time of the blood draw, but fasting serum cholesterol and HDL-C values have been shown to correlate with post-prandial values in both normal controls (non-elevated at baseline) and those with baseline hypercholesterolemia [15].

All data examined by this study has already been coded by the main EPESE research center such that each individual has received their own number and is only identifiable by that number and by particular site area (East Boston, Iowa, New Haven, North Carolina). Data meets HIPAA de-identification criteria. The data collection for the EPESE project has been closed at all sites in 1991-2, but the mortality continued to be recorded and coded past that time (as outlined under Aim 1: Mortality section below) by the EPESE research center [16].

Analysis

AIM 1: To determine if HDL-C levels and HDL-C to total serum cholesterol ratios are prognostic for cardiovascular morbidity and mortality in the entire EPESE population with serum samples

The major variables of this research to assess the predictive value of HDL-C and HDL-C to total cholesterol ratios will be determined as follows:

- Age: "elderly" will be defined as individuals age 65 and older
- HDL Cholesterol: The ratio of HDL-C to total serum cholesterol will be calculated. HDL-C will be stratified by sex and further broken down into 3 groups

  For men: <=37 mg/dL, 38-47 mg/dL, >47 mg/dL [5]

  For women: <=40 mg/dL, 41-50 mg/dL, >50 mg/dL [5]
- Total Cholesterol: Will be stratified into 3 groups <200 mg/dL, 200-240 mg/dL, and >=240 mg/dL [5]
- Triglycerides: Will be stratified into 2 groups <150 mg/dL and >150 mg/dL
- Mortality: A mortality surveillance system is in place at each EPESE center. Information indicating a death may be acquired from obituary notices, hospitalization records, proxy information or other sources. Death certificates are obtained at all centers and the cause of death is reviewed and coded. Mortality (overall survival) will be considered the ultimate end point with the alternate end point of cardiovascular event-free survival.

Mortality will be grouped by survival at 1 year, 5 years and 10 years.

AIM 2: To evaluate the degree to which HDL-C levels and HDL-C to total serum cholesterol ratios are associated with outcomes in those with prior cardiovascular history (recurrence) vs. those without prior history (new events)

The most frequently utilized co-variants in EPESE cohorts include age, systolic blood pressure, presence of stable angina, history of medically treated hypertension, smoking history and history of diabetes mellitus and myocardial infarction [5]. Co-variants selected from following descriptively reported data will be used to determine and adjust for additional risk factors of cardiovascular disease in a multi-variable logistic regression model:

- Clinical History*:* Age, hypertension, diabetes mellitus, prior MI, prior heart failure, current smoker, history of cerebrovascular disease, peripheral vascular disease, and hypercholesterolemia
- Behavioral Covariates*:* Pack-years of smoking; body mass index; alcohol consumption in the past month; physical activity

AIM 3: To determine if HDL-C levels and HDL-C to total serum cholesterol ratios correlate with other outcome measures of overall health status including number of chronic conditions, depressive symptoms, cognitive and physical functioning

Scored components of health status will be used to determine participant's overall functioning which will be examined in the context of HDL-C and HDL-C and serum cholesterol ratios. The following health status assessments are descriptive reports obtained through a systematic interviewing process of EPESE participants:

- Health Status: Health status includes the number of chronic conditions (high blood pressure, heart attack, stroke, diabetes, cancer, a broken hip, or other broken bones); depressive symptoms (Center for Epidemiologic Studies Depression scale score; cognitive function (short portable Mental Status Questionnaire score); and physical function measured with three self-report scales looking at basic activities of daily living, gross mobility, and more difficult tasks.

Since elderly population has the greatest risk of morbidity and mortality from cardiovascular disease, this population would obtain

the most benefit from an easy means of assessing risk and implementing an appropriate intervention. HDL-C and its relationship to total cholesterol is good candidate for assessing risk of cardiovascular disease in an elderly population since it has been shown to have an excellent prognostic value in a middle-age population, is simple to obtain with a blood test, and is a potentially modifiable risk factor through lifestyle and/or pharmaceutical intervention. By utilizing the vast data available in EPESE, the value of HDL-C and HDL-C to total cholesterol ratios in assessing risk can be examined in those with existing cardiovascular disease and those with a new onset. By determining the prognostic value of these simple blood tests, clinicians could better assess elderly patient risk for new or recurrent cardiovascular disease and act to appropriately manage or prevent its potential morbidity and mortality.

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