ASSOCIATION OF OBSTRUCTIVE AIRWAY DISEASE AND LUNG FUNCTION WITH INCIDENT HEART FAILURE, AND OPTIMAL PREDICTION OF HEART FAILURE IN COMMUNITY SETTINGS: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

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ABSTRACT

Sunil K. Agarwal, MD, MPH: Association of Obstructive Airway Disease and Lung

Function with Incident Heart Failure, and Optimal Prediction of Heart Failure in

Community Settings: The Atherosclerosis Risk in Communities Study

(Under the direction of Gerardo Heiss, MD, PhD)

Background: This epidemiologic investigation of heart failure (HF) has two components, one focused on airway disease as a putative antecedent factor to HF and the other centered on the prediction of HF as a means toward reducing the growing burden of HF in the population.

Methods Forced Expiratory volume-1 second (FEV1) and covariates were measured for the ARIC cohort in 1987-89. Incident HF was ascertained annually from hospital records and death certificates. Cox proportional hazards models were used to derive a risk score to predict 10 years risk of HF. Area under curve (AUC) and Net Reclassification Improvement (NRI) were estimated as measures of discrimination.

Results Over an average follow-up of 14.9 years, 1369 (10%) ARIC participants free of HF at baseline had incident HF. The hazard ratios (HRs) for HF increased monotonically over descending quartiles of FEV1. The associations were seen in each of cigarette smoking strata, inclusive of never-smokers. After multivariable adjustment for traditional cardiovascular risk factors at baseline, the HRs of HF and their 95% confidence intervals (CI) comparing the lowest with the highest quartile of FEV1 were 3.91(2.40, 6.35) for white women, 3.03(2.12, 4.33) for white men, 2.11(1.33, 3.34) for black women and 2.23(1.37, 3.59) for black men. The multivariable adjusted hazards of HF were higher in those with FEV1/FVC < 70% vs. ≥ 70%: HR 1.42 (95% CI 1.22, 1.68).

The ARIC HF risk score included information easily available to the primary care physician including COPD. The estimated AUC of the ARIC HF risk score was 0.810(optimism-corrected = 0.808), 95% CI = 0.807, 0.813. It was higher than AUC estimated using variables from the Framingham risk score(0.762) and the ABC risk score(0.784). Overall classification using the ARIC HF risk score

improved for 23.5% individuals relative to the Framingham, and 12.8% relative to the Health-ABC classification.

Conclusions   In this population-based cohort, low FEV1, and obstructive respiratory illness were strongly and independently associated with incident HF. The underlying mechanisms may include diastolic-dysfunction, cor-pulmonale, silent-CHD, and require exploration. The ARIC HF risk score performs better than extant scores and may improve risk prediction of HF in the community.

Dedicated to my teachers: nature, parents, mentors, instructors, patients, friends,

and students.

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LIST OF ABBREVIATIONS

ACC American College of Cardiology

AHA American heart Association

ARIC Atherosclerosis Risk in Communities

AUC Area Under the Curve

BMI Body mass index

BNP B-type natriuretic peptide

BP Blood pressure

CAD Coronary artery disease

CHD Coronary heart disease

CHS Cardiovascular Health Study

CI Confidence interval

CVD Cardiovascular disease

DAG Directed acyclic graph

FEV1 Forced expiratory volume in 1 second

FVC Forced Vital Capacity

GOLD Global Initiative for Chronic Obstructive Lung Disease

HF Heart failure

HDL-C High-density lipoprotein cholesterol

HR Hazard ratio

ICD International Classification of Disease

ICD-9-CM International Classification of Disease, 9th revision, clinical modification

ICD-10-CM International Classification of Disease, 10th revision

ICR Interaction contrast ratio

IR Incidence rate

LDL-C Low-density lipoprotein cholesterol

LRT Likelihood ratio test

LVH Left ventricular hypertrophy

MD Maryland

MI Myocardial infarction

MN Minnesota

MS Mississippi

NIH National Institute of Health

NC North Carolina

NPV Negative predictive value

NRI Net Reclassification Improvement

PPV Positive predictive value

RCT Randomized controlled trial

ROC Receiver operating curve

RR Relative risk

PHA Proportional hazards assumption

PY Person-years

SD Standard deviation

SE Standard error

Q 1 First quartile

Q 2 Second quartile

Q 3 Third quartile

Q4 Fourth quartile

Chapter I

SPECIFIC AIMS

This doctoral research is set out with two primary goals. The first examined whether obstructive airway diseases are associated with higher incidence of heart failure in a middle aged cohort of black and white, men and women in four US communities. To this end, the presence of airway obstructive disease at baseline was ascertained using self reports and measured lung function, and classified according to Global Initiatives for Obstructive Lung Disease classification. In addition, the relationship between stature-adjusted continuous lung function measures, i.e., forced expiratory volume – 1 second (FEV1) and incident heart failure was examined. Further, the potential of inflammation as a mediator of the putative association was examined using an available set of systemic markers of inflammation. Finally, the sensitivity of the putative association to measurement error in the outcome was explored.

The second goal developed a novel heart failure risk prediction function, the "ARIC heart failure risk score" and compared it with extant risk functions, and also examined the potential of novel biomarkers predictive of HF to improve the

ARIC heart failure risk score. The external validity of the extant heart failure risk scores, the Framingham Heart Study and Health ABC Study scores, were examined in a cohort of African American and white middle-aged men and women. Follow-up for new-onset hospitalization and mortality attributed to heart failure was available from 1996-98 through 2005.

Novel estimation methods were used to evaluate the performance of the ARIC heart failure risk score relative to previously published methods.

The specific aims are listed below:

1a **Test the association of lung function measures (FVC, and FEV1) with risk of incident heart failure (HF).**

> **i)** **Evaluate whether the above relationship differs by smoking status.**

> **ii)** **Evaluate whether the above relationship is explained by coronary heart disease at baseline or during follow-up**

> **iii)** **Evaluate whether the above relationship is attenuated after adjusting for potential markers of inflammation/ hypercoagulability, and maximal inspiratory pressure (MIP), as these may be intermediary in the hypothesized associations.**

1b **Test the association between baseline COPD (self report of productive cough, self report of physician diagnosis, and GOLD classification) with risk of incident HF.**

2a   Examine the validity of the extant HF risk scores in a population based cohort of middle aged black and white, men and women from four US communities.

2b   Derive a risk function with elements readily available to general practitioners to predict the 10 year risk of HF in a community based cohort of middle aged men and women.

1) Compare its ability to discriminate between those who had HF from those who didn't (discrimination) and concordance between expected and observed events by deciles of risk.

2) Compare the performance of the ARIC HF risk score with the risk functions estimated in this study population using the variables from extant risk functions.

3) Examine the performance of the ARIC HF risk score based on net reclassification improvement relative to the extant risk functions.

2c   Evaluate the incremental value of cystatin-C and hs-CRP for the prediction of HF.

Chapter II

BACKGROUND AND SIGNIFICANCE
2A. HEART FAILURE: Diagnosis, risk factors, predictors, and burden

2.A.1 Public Health Burden of Heart Failure

Heart Failure (HF) stands out as a major public health problem in the economically developed nations (Garg, Packer et al. 1993; Rosamond, Flegal et al. 2008). Its incidence approaches 10 per 1000 population after age 65 years (Lloyd-Jones, Larson et al. 2002), Despite improvements in medical management and advances in therapy, its incidence and prevalence have increased (Roger, Weston et al. 2004). Overall, it is estimated that about 5 million patients have HF in the U.S., and about 500,000 individuals are diagnosed with HF for the first time each year (Rosamond, Flegal et al. 2008). Its prognosis is grim (26% mortality at one year)(Levy, Kenchaiah et al. 2002) and the costs of its treatment exceed those for coronary artery disease and cancer combined (5.4% of the total US health care expenditures)(O'Connell and Bristow 1994).

Nearly 300,000 patients are estimated to die of HF as a primary or contributory cause each year (Hunt, Abraham et al. 2005) – which probably represents a an underestimate of large magnitude(Anthony, Rosamond et al.

2009). Although age-adjusted mortality rates attributable to HF show a declining trend, the overall mortality has increased with the aging of the population (1998). The average one-year survival for individuals with ACC/AHA stage D HF is less than 20% (Ammar, Jacobsen et al. 2007), a prognosis worse than that of many common cancers (Hobbs 2002). The 2004 overall death rate per 100 for HF was 19.1, with the highest rate among black males (22.9) and the lowest in white females (18.3)(Rosamond, Flegal et al. 2007). Importantly, sudden cardiac death is common (40% of all deaths) among individuals with HF (Uretsky and Sheahan 1997).

Healthcare burden and cost HF is the leading indication for hospitalization in the United States among patients older than 65 years. Hospital discharges with an HF diagnosis rose from 399,000 in 1979 to 1,009,000 in 2004 (Rosamond, Flegal et al. 2008). Of the estimated 22.6 million hospitalizations among >45 years old, HF was a diagnosis seen in about 19.2% of the hospital discharges. It was a primary discharge diagnosis in 4.7% (n=1.05 million) and secondary in 14.5% (n = 3.3 million) (unpublished; Agarwal, McNeill et al. 2009).

Treatment costs for HF amount to 5.4% of the total health care expenditure (O'Connell and Bristow 1994). In 2001, $4.0 billion ($5912 per discharge) was paid to Medicare beneficiaries for CHF (Rosamond, Flegal et al. 2007; Rosamond, Flegal et al. 2008). The estimated direct and indirect cost for HF in the United States was $33.2 billion in 2007 (Rosamond, Flegal et al. 2008).

2.A.2 The Challenge of Heart Failure Diagnosis in Primary Care Settings

HF is a clinical syndrome and the result of complex pathological processes that culminate in the failure of the heart to circulate blood at normal pressure to meet the body's need (Braunwald, Zipes et al. 2001). For diagnostic purposes the ACC/AHA advocate consideration of appropriate symptoms and signs when present, plus objective evidence and response to treatment when in doubt (Hunt, Abraham et al. 2005). Though sensitive, the signs and symptoms of HF have low specificity (Rutten, Cramer et al. 2006). This problem is accentuated due to their high prevalence in the elderly, the obese and in women (Dahlstrom 2005). Importantly, unrecognized ventricular dysfunction and HF are frequent among individuals with comorbidities, many of whom have manifestations such as dyspnea and pedal edema (McDonagh, Morrison et al. 1997; Mosterd, Hoes et al. 1999). There is ample evidence of misdiagnosis by physicians when objective criteria are used (Remes, Miettinen et al. 1991). Thus, a definitive diagnosis of HF entails the use of cardiac imaging (e.g. echocardiography and radio-nuclide ventriculography to assess left ventricular dysfunction), and referral to a cardiologist.

Heart failure is broadly classified as systolic or diastolic in nature. At this point there is no standardized definition of diastolic dysfunction; it is mostly a diagnosis of exclusion of systolic heart failure (ejection fraction ≥50%) more commonly called as heart failure with preserved ejection fraction occurring within

72h of an HF event, i.e. the presence of symptoms of cardiac congestion and response to diuretics (Vasan and Levy 2000). However, recent studies have shown that as compared to systolic failure, diastolic failure is equally prevalent (Bursi, Weston et al. 2006), carries a similarly poor prognosis (Owan, Hodge et al. 2006), and requires treatment of comparable cost(Liao, Jollis et al. 2006). Population based studies have further reported that at least half of the individuals with systolic or diastolic left ventricular (LV) dysfunction on echocardiography have never been diagnosed as having heart failure (McDonagh, Morrison et al. 1997; Mosterd, Hoes et al. 1999).

To manage their patients well, primary care practitioners should be better able to recognize and quantify HF risk early by evaluating an individual's risk of decompensation requiring hospitalization for HF. To this end, risk score functions may be helpful for timely referral and diagnosis in patients at high risk of HF.

2.A.3. Major known risk factors

Coronary Heart disease, Diabetes, Hypertension, Left ventricular hypertrophy, valvular heart disease are considered to be common and potentially modifiable risk factors of Heart Failure. Other common and increasing prevalent risk factors include higher body fat (reflected by high BMI or Waist Circumference), sleep apnea, and other traditional risk factors for CHD i.e., smoking, dyslipidemia are also distal risk factors for heart failure.

2.A.4 Predictors for incident heart failure in the community

2.A.4.1 The role of history, symptoms, signs and ECG. Considerable information is available to providers of primary care to assess and predict an individual's risk of developing symptomatic HF, such as demographic information, medical history, physical examination, a basic biochemistry panel, and an ECG. The predictive accuracy of various co-morbid conditions, symptoms, signs and ECG patterns has been studied in both clinical and population settings, mostly in Caucasians. It has been reported that most of the symptoms and signs commonly associated with HF are sensitive but non-specific, while the less prevalent or subtle ones occurring in moderate to severe disease are specific, but less sensitive. A normal ECG is highly specific on the other hand, virtually ruling out HF or LV dysfunction (Rihal, Davis et al. 1995). Further, abnormal ECGs have been shown to have good sensitivity, i.e., 73-94% in a meta-analysis (Khunti, Squire et al. 2004) and 81% in the community-based EPICA study (Fonseca, Mota et al. 2004). Thus, a combined use of a patient's history, physical exam, basic laboratory investigations and ECG may provide an optimum tool for patient risk stratification. This has been attempted to a limited extent on data from two cohorts, as discussed below. Studies using ARIC cohort data have found ECG parameters (Rautaharju, Prineas et al. 2007), renal function (Kottgen, Russell et al. 2007), diabetes (Pazin-Filho, Kottgen et al. 2008), and respiratory illness (Agarwal, Loehr et al. 2009) to be potential risk factors for incident HF.

2.A.4.2 The potential role of biomarkers In recent years, biomarkers have been the focus of research in cardiovascular diseases to improve diagnosis. Despite their considerable potential and the low specificity of many other risk factors, biomarkers have not yet been considered for HF risk stratification.

2.A.4.2a. High sensitivity C-reactive protein (hs-CRP) CRP is an acute phase protein produced by liver in response to increase in several pro-inflammatory cytokines, especially interleukin 6 and tumor necrosis factor. It is a well validated, systemic marker of inflammation. Several reports have suggested its independent association with incident HF(Kardys, Knetsch et al. 2006; Bahrami, Bluemke et al. 2008; Williams, Shah et al. 2008).

2.A.4.2b. Cystatin C It is a cysteine protease inhibitor secreted by most human cells and metabolized in the proximal tubules in kidney after being freely filtered at the glomerulus. It is presently considered a more sensitive marker of mild renal dysfunction than creatinine and has been found associated with incident heart failure(Sarnak, Katz et al. 2005; Moran, Katz et al. 2008).

2.A.4.2c N-terminal pro-B-type natriuretic peptide (NT-proBNP) Plasma B-type natriuretic peptide (BNP) and its amino terminal pro-hormone (NT-proBNP) are associated with sub-clinical cardiac structural and functional abnormalities, and with incident HF in the general population (Wang, Larson et al. 2004; de Lemos and Hildebrandt 2008). NT-proBNP may thus enhance an efficient and simple

risk prediction of HF in the community (Ng, Geeranavar et al. 2004). Although the European Society of Cardiology has recently introduced BNP in the diagnostic algorithms of HF (Swedberg, Cleland et al. 2005), AHA awaits further investigations to clarify their role (Hunt, Abraham et al. 2005).

2.A.4.2d. High Sensitivity Troponin T (hs-TropT). Cardiac troponins in serum are highly specific markers of myocardial injury commonly used for the diagnosis of acute ischemic coronary events (Antman, Tanasijevic et al. 1996; Donnelly and Millar-Craig 1998; Lindahl, Toss et al. 2000; Apple, Wu et al. 2005). Several studies have reported an association between increased concentrations of troponin measured in blood and HF prevalence, severity and prognosis (Sato, Yamada et al. 2001; Sato, Taniguchi et al. 2002; Setsuta, Seino et al. 2002; Horwich, Patel et al. 2003; Ishii, Cui et al. 2003; Del Carlo, Pereira-Barretto et al. 2004), although concentrations are generally lower than those seen in patients with acute coronary syndromes (Aviles, Askari et al. 2002). The potential association of low levels of troponin T detected with highly sensitive assays with incident HF awaits investigation.

B. COPD: definition, patho-physiology, and burden

B.1 Definition. Chronic obstructive pulmonary disease (COPD) is characterized by non- or poorly reversible expiratory airflow limitation. The airflow limitation is usually progressive(Pauwels, Buist et al. 2001). Epidemiologic studies have for long used a questionnaire-based definition i.e., the presence of productive

sputum for at least 3 months during two consecutive years. There are two subtypes of COPD present in individuals to varying extent, i.e., chronic bronchitis and emphysema. Thus, varying degrees of pathological small airway obstruction and destruction of parenchyma constitute COPD.

The American Thoracic Society (ATS) recommends the use lung function quantified by spirometry to define COPD. Forced vital capacity (FVC) refers to the maximum amount of air an individual can exhale after maximal inspiration. Forced expiratory volume in 1 second (FEV1) refers to maximum volume of air an individual can exhale in 1 second after maximal inspiration. A reduced ratio of FEV1 to FVC is an indicator of obstruction to air outflow during the early phase of exhalation. Figure 1 depicts the main volumes and capacities derived from spirometry readings.
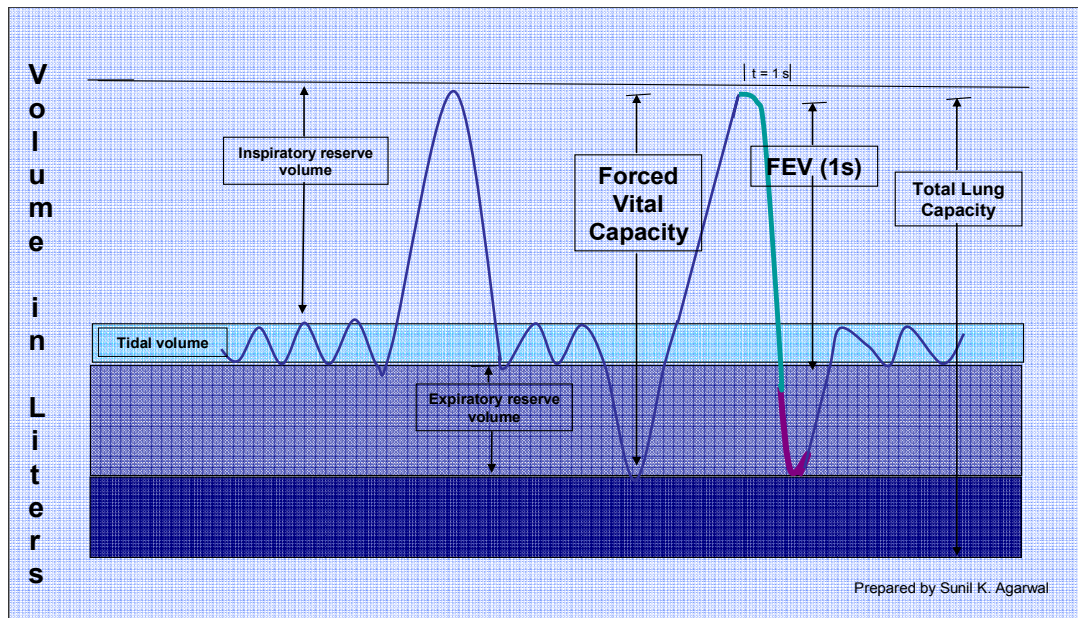
Graphical representation of lung volumes and capacities (combination of two or more volumes). FEV1 = Forced Expiratory Volume (1second)

Figure 1. Schematic depiction of Forced Expiratory volume in 1 second (FEV1) and Forced Vital Capacity.

A lower peak flow is sensitive but not specific to diagnose COPD since it may be caused by other lung diseases as well as by poor effort.(Pauwels, Buist et al. 2001). Thus, there has been emphasis on the use of FEV1/FVC ratio for clinical purposes. A cut point of 0.7 for this ratio has been suggested to define presence of COPD, after verifying that this restriction is irreversible by using a bronchodilator. However, this ratio and its cut point may not be appropriate for all ages due to the age-related decline of volumes, which affects FEV1 more than FVC. Thus, in this research we have focused on severe COPD which can be safely assumed to be age independent. The staging of COPD as suggested by the GOLD Executive Committee report is shown in Table 1.

Table 1. Global Initiative for Chronic Lung Disease Classification for lung diseases		
Lung disease	GOLD staging	Definition
No lung disease		No chronic respiratory symptoms & no lung function abnormality
At risk of COPD	**0**	Chronic respiratory symptoms & no lung function abnormality
Restrictive		FEV1/FVC >= 0.70 and FVC < 80% predicted
Mild COPD	**1**	FEV1/FVC <0.70 and FEV1>=80% predicted
Moderate COPD	**2**	FEV1/FVC <0.70 and FEV1>=50 to < 80% predicted
Moderate/severe COPD	**3-4**	FEV1/FVC <0.70 and FEV1<50 predicted
GOLD: Global Initiative on Lung Disease classification The ARIC study didn't evaluate response to bronchodilator hence the levels are based on "pre-bronchodilator'' functions. Also total lung volume was not available, thus it was difficult to define strict category of restrictive disease.		

B.2 Burden of Heart Failure. In contrast to the decrease in death rates from coronary heart disease and stroke the unadjusted death rates from COPD per 100,000 residents of the US has increased from 2.1 in 1950 to 40.2 in 2004.(NHLBI 2007) Further, these death rates are higher among whites (1/3rd for males and 2/3rd for females) than blacks. (NHLBI 2007) Among industrialized nations the rates were lowest for Japan in 2004, while US ranked among the nations with higher rates.

B.3 Pathophysiology of COPD. Although most patients with lung disease present chronic respiratory symptoms including productive cough before COPD, this is not always the case. The chronic airway disease components consist of mucus hypersecretion, ciliary dysfunction, airflow limitation. This, along with

alveoli destruction leads to subsequent pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor-pulmonale (Pauwels, Buist et al. 2001).

There is a gradual decline with pulmonary function (volumes) with age accompanied by mild inflammation called senile emphysema. In a recent review, Iko et al. suggested that COPD represents a state of accelerated decline in lung function mediated by increased systemic and local inflammation (Tkac, Man et al. 2007). Smoking, air pollution, and exposure to noxious air stimuli are known, strong risk factors for the development of COPD. Other risk factors such as absence of alpha-1 anti-trypsin enzyme are uncommon.

C. COPD/Lung function and Heart Failure

HF is common among patients with chronic obstructive pulmonary disease (COPD) and vice versa (Dahlstrom 2005; Rutten, Cramer et al. 2006). As seen in Table 2, in a nationally representative sample of about 20% of all hospitalizations in community hospitals across the US, a concomitant ICD code of COPD was present in 34.6% of the hospitalizations with an ICD code for HF (Agarwal, McNeill et al., unpublished).

Table 2. Common comorbidities seen in hospital discharges among ≥ 45 years from the community hospitals in the United States: The National Inpatient Sample 2006 (Agarwal, McNeill et al. 2009)

	HF code in the discharge diagnosis		
Condition Definition	Primary position	Secondary position	Absent
Coronary atherosclerosis	0.54	0.46	0.25
Cardiac dysrhythmia	0.44	0.41	0.16
Essential hypertension	0.43	0.40	0.49
Chronic obstructive pulmonary disease	0.31	0.33	0.15
Diabetes mellitus without complication	0.30	0.25	0.19
Disorders of lipid metabolism	0.27	0.23	0.26
Heart valve disorders	0.27	0.18	0.06
Hypertension with complications and 2* HTN	0.23	0.24	0.08
Deficiency and other anemia	0.22	0.23	0.16
Fluid and electrolyte disorders	0.22	0.32	0.21
Peri/endo/myocarditis or cardiomyopathy	0.21	0.12	0.02
Chronic renal failure	0.20	0.18	0.06
Conduction disorders	0.20	0.13	0.05

COPD complicates both the diagnosis and treatment of HF. Both COPD and HF may present with symptoms of dyspnea and orthopnea. If beta blockers are indicated in a patient with HF, the presence of COPD, necessitates the use of low-dose cardio-selective beta blockers with slow titration(Cazzola and Matera 2008).

Several lines of research point to a common soil for COPD and HF. A vast literature suggests a higher cardiovascular mortality in individuals with COPD and reduced lung function. Factors such as chronic muscle wasting, autonomic dysfunction, systemic inflammation(Schroeder, Welch et al. 2003), or oxidative stress(Mannino, Doherty et al. 2006) may be responsible for this

increased risk. In the context of diseases affecting structure and function of lung pulmonary hypertension and cardiac dysfunction i.e. cor-pulmonale is well known(Budev, Arroliga et al. 2003). In addition, influenza vaccination, primarily reducing serious lung disease and mortality(Nichol, Margolis et al. 1994), also prevents new onset of HF(Davis, Taubert et al. 2006). A schematic representation of several pathways leading to Heart Failure is shown in figure 2.
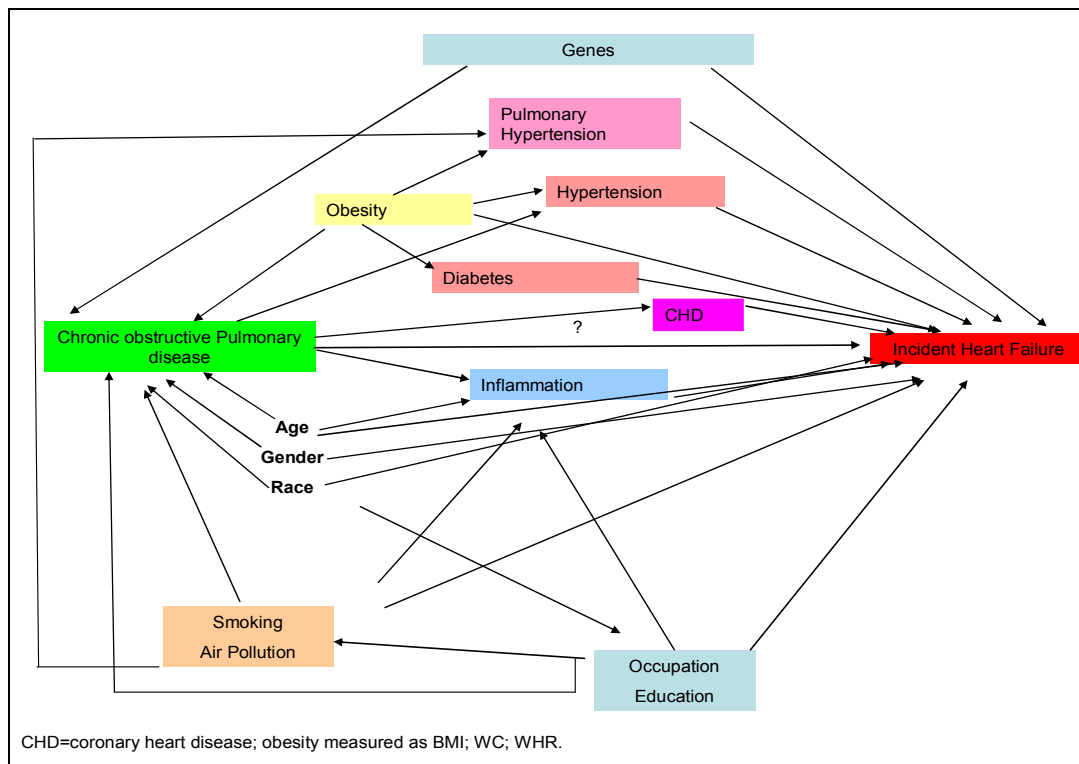
Figure 2. Conceptual framework of factors linking COPD and heart failure. This is not a Directed Acyclic Graph as several constructs may effect each other at the same time as well as temporally thus have potential to act as both confounder as well as intermediary.

D. Studies of COPD /Lung function) as a Risk Factor for Heart Failure

In a longitudinal study published in 1974, Kannel et al. examined the relationship between forced vital capacity and incident heart failure in the Framingham Heart Study. The authors reported that both a persistently low and a recent fall in vital capacity were associated with increased risk of HF. However, they did not find an association between obstructive disease (FEV1/FVC) and incident HF. In a case control study published in 2005, Sidney et al. have reported an association between COPD associated with incident HF, RR = 3.75 (95% CI: 3.39, 4.15) using a large administrative dataset (Kaiser Permanente Medical Care Program).

E. Validation of ICD code '428.x' for the diagnosis of HF

In her thesis, available electronically (UMI: 3322231), Dr. Laura R. Loehr summarizes five studies examining the validity of ICD codes for defining heart failure(Loehr 2008). There was considerable variability in the estimates from these studies, and the lack of a uniform gold standard is a contributor to this. The ARIC study heart failure surveillance results provide a better framework to understand this issue since HF status is ascertained using several standardized classification criteria and a meticulous review by a panel of physicians. In a sample of hospitalizations with suspected CHD, the PPV of HF diagnosis was 83.5% while sensitivity was 62.8%, when using a physician diagnosis or pulmonary edema on X-ray as gold standard [136. A hospital discharge diagnosis of ICD 9-DM- 428.x was reported to have a positive predictive value of 94.3% when compared to the Framingham criteria (Lee, Donovan et al. 2005).

In the ARIC HF surveillance study based on a sample of hospitalizations with high suspicion of HF, the PPV of an ICD code '428.x' for HF classified according to ARIC study procedures was 77%, and its sensitivity was 95% (Rosamond, Chang et al. 2009). In the same study the corresponding PPV and sensitivity of an ICD code '428.x' for HF defined by the Framingham Heart Failure criteria was 0.78, and 0.83, respectively.

F. Risk score functions and their utility

2.F.1 <u>Early diagnosis improves outcomes.</u> While there has been progress in the therapy of HF leading to better survival during the last decades, many researchers agree that future efforts need to be directed towards early detection of ventricular dysfunction and prevention of symptomatic heart failure(Fonseca 2006). Highlighting the importance of early diagnosis and treatment in individuals with LV systolic dysfunction, the Study of Left Ventricular Dysfunction (SOLVD) trial showed that patients randomized to enalapril (an ACE inhibitor) had lower late mortality and lower serious CV morbidity as compared to placebo who also received enalapril at the trial close out (Ahn, Jong et al. 2006). This becomes particularly important in light of the high proportion of sudden cardiac death among individuals with mild HF (Uretsky and Sheahan 1997). Thus, an early and accurate HF diagnosis can be viewed as the cornerstone of improved patient outcome.

2.F.2 <u>Early diagnosis/referral in primary care setting improves outcomes</u>. Most patients with HF present for the first time to general practitioners (GPs) and are mostly managed by them (Fowler 1997). Results of a qualitative study involving focus groups of 30 GPs in four primary care settings in the UK showed that lack of confidence in establishing diagnosis, rapidly changing knowledge and doubts about the applicability of research to primary care settings were identified as main barriers to providing standard care to patients with HF in the community (Fuat, Hungin et al. 2003). Whereas accurate diagnosis is crucial for effective management, many practitioners at the primary care level rely on clinical elements to diagnose heart failure without further investigation, thus deviating from the available guidelines (Fonseca 2006). Furthermore, the importance of early diagnosis and treatment of left ventricular systolic dysfunction was not fully appreciated among general practitioners (Mair and Bundred 1996). A review of HF patients' charts in Netherlands reported that although general practitioners had more elderly and female patients, they asked for fewer tests and also prescribed potentially beneficial medications less often compared to cardiologists (Rutten, Grobbee et al. 2003). Similarly, a large multinational European survey of patients with HF reported that while 92% of the treating physicians asked for an electrocardiogram (ECG), only 45% asked for an echocardiogram (Cleland, Cohen-Solal et al. 2002). Thus, primary care practitioners, though providing most of the care for HF, confront difficulties in the recognition and diagnosis of HF.

2.F.3 <u>Risk score functions as an aid to stratification and referral</u>. Clinical prediction models combine patient characteristics to predict the probability that a particular disease state will occur. Risk scores based on an optimal set of predictors demonstrably predict the probability of incident cardiovascular events in various populations (D'Agostino, Grundy et al. 2001). Their use for the risk management of CHD has been strongly encouraged in the NCEP- ATP III guidelines (2001), and made available by NHLBI for use in clinical practice . Risk score functions may be particularly useful in the identification of groups at intermediate risk and they are now recognized as essential in efficiently identifying likely candidates for CHD (Kannel, D'Agostino et al. 2004).

Unlike most manifestations of CHD, ventricular dysfunction remains masked and undetected in majority of its carriers, though early identification and proactive management could improve health outcomes. Further, comorbidities – particularly those affecting the lungs (Kannel, Seidman et al. 1974) or kidneys (Kottgen, Russell et al. 2007) – may contribute to or precipitate cardiac decompensation in the absence of manifest CHD. Particularly in this context, various biomarkers may be of value as elements of risk score functions.

2.F.4 <u>Strengths and limitations of the existing risk functions</u>. The HF risk score function derived by the Framingham Heart Study (FHS) investigators and a recently published risk score from the Health, Aging, and Body Composition (Health ABC) study are the only published tools available for predicting incident

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HF. Their main features are summarized in **Table 3**. The FHS is restricted to white examinees and provides a full score that includes elements with limited availability to primary care practitioners such as forced vital capacity and X-Ray.

Table 3. Comparison of study design and elements for the existing and proposed HF risk score

	FHS complete	Health ABC score	ARIC Study
Study characteristics			
Sampling	Community based	selected: relatively healthy	community based
Age at baseline (range)	45-94y	70-79y	52-75y
Sample size	5209(?, not mentioned)	2935	10781
Follow up HF events	486	258	1000+
Risk predicted for years	4	5	4, 5 and 10
% Black	0	40	23
Outcome ascertainment using	Framingham criteria	Adjudicated ICD codes	Adjudicated ICD codes
Methods used	Pooled logistic regression	Cox regression	Cox reg. and newer methods
Subset analysis	None	Group with CHD, HTN, VHD	Race, and gender
Internal validation	None	Bootstrapping	Bootstrapping
External validation tested for		FHS abbreviated	FHS and Health ABC study
External validation study	Health ABC cohort	None	--------
Data elements used			
Age	X	X	X
Left ventricular hypertrophy	X	X	X
Vital capacity	X		X
Heart rate	X	X	X
Systolic blood pressure	X	X	X
Coronary heart disease	X	X	X
Valvular disease (auscultation)	X		X
Diabetes	X	Fasting blood glucose	X
Cardiomegaly (X-Ray)	X		
Smoking status		X	X

Albumin	X	X
Creatinine	X	X
Cystatin C		X
Prolonged QRS interval		X
C reactive protein		X

Although the Health ABC study has validated the former score in a population of older adults, an external validation of the Framingham HF risk score in a similar population is pending since external validation in an independent test data set is an accepted requisite before the use of such models can be recommended (Ripley 1996). The Health ABC cohort includes older black and white participants, but no information on calibration or discrimination of the score for blacks was provided. The Health ABC study tested some variables not included by FHS, i.e. smoking, serum albumin and creatinine. Both studies included left ventricular hypertrophy, which is uncommon in middle aged participants and not easily accessible to primary care physicians. It is also relevant to note that conditions of high prevalence such as other ECG abnormalities, respiratory illness, and obesity deserve to be tested for their potential ability to modify the basic risk function estimated from these data. Hence, an external validation of both the risk scores and an assessment of the relative importance of the variables used in their calculation represent timely and informative contributions. For reasons mentioned above, an HF risk score that performs well in the primary care setting would have wide applicability and potential impact. It's noteworthy that each of the above studies had a limited number of events, thus restricting the statistical power available to test the incremental value of putatively important predictors. Further, better methods are

being investigated for prediction with censored data (Chambless and Diao 2006), and reclassification is relied on at present to assess the performance of risk functions more so than on traditional approaches based on an increase in the area under the ROC curve (Pencina, D' Agostino RB et al. 2008; Pepe, Feng et al. 2008). As evidenced by risk predictions for incident CHD, prognostic statements for 5 to 10 years are of value in the prevention and management of chronic disease. Of note, the Framingham and Health ABC studies did not provide information on long term risk prediction beyond 4-5 years. Lastly, the additional use of novel biomarkers in these equations or their calibrated versions will be a timely and potentially important innovation by this study.

G. Methods to Adjust for Bias

The primary concerns with bias in this project apply to misclassification of hospitalized HF and their potential contamination with COPD exacerbations given the many overlapping signs and symptoms(Hawkins, Petrie et al. 2009), and optimism in the estimation of primary discrimination statistics of the HF risk functions estimated in the ARIC cohort since the derivation and testing samples are the same.

The first concern regarding outcome misclassification in an exposure-outcome study was partly resolved by sensitivity analysis. To evaluate whether our findings may be a result of misclassification of incident HF, sensitivity analyses were conducted as follows: a) analyses excluding participants with self

reported COPD; b) replicate analyses excluding participants with prevalent CHD; c) excluding both baseline COPD and prevalent CHD; and d) , analyses that excluded those with acute exacerbation of COPD during HF hospitalization (n= 78), those with acute exacerbation of COPD or respiratory failure (n=229) during a hospitalization coded as HF, and e) censoring those with acute exacerbation of COPD or respiratory failure (n=229) during HF hospitalization. The second concern, namely optimism in the estimation of the AUC was addressed by subtracting an estimate of optimism derived by using 1000 bootstrap samples from the AUC estimate.

H. Summary and public health significance

Heart Failure is a common condition in economically developed countries and at the root of a large and growing burden of disability, early death, and health care expenditures. Despite large allocations of resources to its medical care, its prognosis remains grim. Identification of novel risk factors and pathways for HF may prevent or delay decompensated, hospitalized HF and also motivate the development of new therapeutic targets. While the rate of mortality attributable to heart disease is declining, COPD remains a primary public health concern as well as the only condition with an increasing of mortality in the U.S. This study tests association between reduced lung function and incident HF after adjustment for potential confounders in a large community based cohort. It also explores whether markers of inflammation may be partially explain or be mediator of this association.

HF is mostly managed in primary care settings. It is a clinical syndrome, diagnosed with the aid of a combination of signs, symptoms and laboratory and imaging studies. Owing to the low specificity of individual signs and symptoms it is challenging to diagnose HF early and accurately in community settings. Importantly, early diagnosis and management are beneficial in delaying the occurrence of decompensated HF and of poor outcomes in patients with HF. An accurate risk prediction function may provide important information about an individual's risk of future events. This is particularly important for HF patients as mild, asymptomatic left ventricular dysfunction (systolic as well as diastolic) is common in the community, and a large proportion of individuals with HF suffer sudden cardiac death, even with mildly symptomatic HF. This study evaluates the external validity of the two existing HF risk scores in a large bi-racial cohort of middle-aged men and women in four US communities. Further, this study examines the potential value of few biomarkers in enhancing HF risk prediction functions. Identification of individuals at risk of developing HF can contribute to scheduling of care visits, early referral, proactive management, and improved health outcomes.

Chapter III

METHODS

A.   Study population

The source population that comprises the ARIC study was a community based sample of males and females, ages 45-64 at enrollment, from 4 US communities. The race/ethnic composition reflects that of two communities (seven suburbs of Minneapolis, MN and Washington County, MD) whereas African Americans were over sampled in Forsyth County, NC and Jackson MS participants were restricted to age-eligible African Americans. The over-sampling of African American participants (approximately 27% of the participants at baseline exam) was a deliberate effort to investigate minority health related issues. At baseline, approximately 50% of the participants were female. As the ARIC study was designed to assess sub-clinical cardiovascular disease in a middle aged –population, it was not felt that inclusion of persons under age 45 would contribute to study objectives, thus enrollment was restricted to persons 45 years and older. Racial groups not classified as white or black will be excluded in this study due to their limited numbers at study baseline (n=48).

Table 4. ARIC study population by race at study enrollment

	Black, not of Hispanic origin	White, not of Hispanic origin	Total
Female	2635	6050	8710
Male	1631	5428	7082
Total	4266	11478	15792

B. Protection of Human Subjects

This project used extant ARIC data, and measures covered by the informed consent provided by each study participant. Neither the measures used in these analyses nor the resulting estimates of HF risk are reportable to the cohort members or their providers of medical care. The ARIC study adheres to a well established and standardized data collection protocol, which is reviewed and annually approved by institutional review boards at each participating institution. IRB approval to support this proposed analysis was obtained in September 2008. The ARIC study investigators have approved the release a de-identified data file containing requested variables to the investigator. The investigator has signed a data use agreement indicating that the clinical data, biological materials, modified or unmodified derivatives thereof, will not be used contrary to specifications stated in the study subjects' informed consent. Further, both the studies of this project were approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

C. Ascertainment of heart failure events

The ARIC Study enrolled 15,792 subjects aged 45-64 years in four U.S. communities: Forsyth County, NC; Jackson, MS; seven northwestern suburbs of Minneapolis, MN; and Washington County, MD. Enrollment at the Jackson, MS site was restricted to black residents, while black residents were over-sampled in Forsyth County. Baseline examinations of the cohort were conducted from 1987 to 1989 to collect information about socioeconomic indicators, medical history, family history, cardiovascular risk factors, serum chemistries, ECGs, medication use, and lung volumes. The cohort participated in four examinations including baseline visit, annual telephone interviews and active surveillance of their hospitalizations and death.

D. Incident heart failure event criteria

Incident HF was defined as the first HF hospitalization with an HF discharge code or HF as the underlying cause of death on a death certificate (n=84). Hospital discharge diagnoses were coded using the International Classification of Diseases Code, Ninth Revision (ICD-9, code 428), and deaths were coded using ICD-9 or ICD-10 (codes 428 and I 50, respectively). Cohort follow up for the current analysis ended on 31st December 2005.

E. Measurement of primary exposures:

Lung functions

At the baseline visit, pulmonary function was assessed using a water-sealed Collin Survey II volume displacement spirometer. Spirometry was conducted using American Thoracic Society guidelines(1987). From at least three acceptable readings, of which at least two were reproducible (volumes within ± 5%), a best reading was selected by computer and confirmed by technician. Methodology was standardized across four field centers including training and certification of pulmonary technicians.

COPD

History of respiratory illness was obtained from standardized questionnaire(Ferris 1978) by trained personnel.

F. Baseline covariate definitions

At baseline, prevalent coronary heart disease (CHD) was ascertained by self-report and a 12-lead ECG. Hypertension was defined by diastolic pressure≥ 90 mm Hg or systolic pressure≥140 mm Hg on the average of the last 2 of 3 measurements, or the use of anti-hypertensive medications. Diabetes was defined by the presence of serum glucose level >= 200 mg/dl, an 8-hour fasting glucose level >=126 mg/dl, a self-reported history of physician-diagnosed diabetes, or the current use of hypo/antihyper-glycemic medications. Other medications intake including beta blockers was self-reported or derived from

medicines brought by participants during exam. Cigarette smoking status was defined as currently smoking or a history of ever smoking four hundred cigarettes or more. The average number of cigarettes/day and number of years of smoking reported were multiplied to derive cigarette-years of smoking. Body mass index was defined as the ratio of measured weight (kilograms) and measured height2 (in meters2). Participants identified themselves as belonging to American/Alaskan Indian, Asian, black, or white race.

G. Statistical power analysis

G1. Cox Regression Power analysis was done using a total sample at risk visit 4 = 10781, follow up period = 5 years and 10 years, alpha = 0.05 (two-sided), exposure proportion at baseline = 10% and 40% and median time to event among unexposed = 4.5 and 9 years (conservative).

There is 80% power to detect a hazard of 1.13 when using 5 years follow up and 10% prevalence (conservative for some risk factors like hypertension). Similar, analysis was done by restricting the sample size at baseline to that of African American (n=2425), other parameters being same. For 5 years follow up and a variable with 10% prevalence there is 80% power to detect an alternative HR>1.3. Also, the number of variables fitted in the multivariable model * 10 is less than number of HF(Rothman 2002), hence degrees of freedom available for calculation of coefficients should not be a problem.

Graph showing alternative hazard when 10 % of all or African Americans in the study are exposed and followed up for 5 years
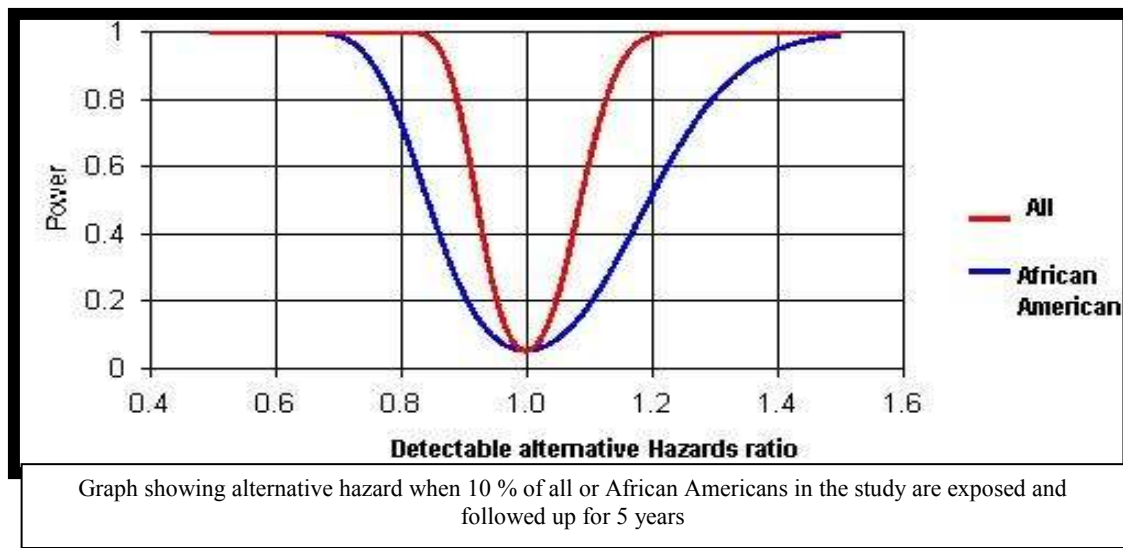
Figure 3. Minimum hazard ratio detectable with study size under range of power.

Hence, there seems to be enough power to identify important predictors using Cox regression. The above power analysis was done using PS software (Schoenfeld and Richter 1982).

G2. Minimum detectable differences in area under curve on a two sided null hypothesis at alpha = 0.05 and beta = 0.2 and 0.1 is shown in table 5. The two study samples shown are for the overall cohort and for African American sub-sample. The estimates make the assumption of a correlation of 0.6 for both false positive and false negative on two risk functions, which is conservative as we expect high correlation. Further, we wish to test one sided hypothesis of whether inclusion of variable improves the AUC, hence these estimates are even more conservative. Also, the two issues of partial AUC, and risk-cut off for decision

making dictate power. Novel methods of reclassification outlined above will provide more power. We will use cut-offs similar to those for coronary artery disease.

Table 5. Area under receptor operating curve: minimum difference in AUC detectable at two values of power

HF	No HF	AUC under null	Min Diff at power = 0.8
1000	9781	0.5	0.023
1000	9781	0.6	0.024
1000	9781	0.7	0.024
1000	9781	0.8	0.025
270	2165	0.5	0.042
270	2165	0.6	0.043
270	2165	0.7	0.044
270	2165	0.8	0.045

Statistical Analysis

SAS, version-9.1 and STATA-IC, version-10 software were used for analysis. A $p<0.05$ for a two-sided test was considered statistically significant. Means (standard deviations) and proportions of characteristics at baseline and follow up HF event rates were calculated for quartiles of FEV1. A higher proportion of blacks and women were in the lower quartiles of FEV1 and FVC; thus all analysis (except for table 7) used race and gender specific quartiles of FEV1.

General consideration of time to event analysis:

A participant susceptible to event of interest is said to be at-risk for the event. In this study, those with prevalent HF were not susceptible to an incident event and thus were removed from the analysis. The duration when someone is

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not susceptible for the event such as person-time before origin, after a non-repeating event of interest such as incident heart failure, and after a competing event such as death and still contributes to person time is said to be contributing to immortal time. The origin in this study was enrollment in the study and then participants were followed every year with an annual follow up interview and surveillance of community hospitals. If a participant enters study prior to becoming at-risk, then the time from study entry to onset of risk is not time at-risk, but is called immortal person-time. Hence, there is no evident immortal person time in the study. Most of the individuals censored in the study were due to administrative censoring or due to death. We can assume with some confidence that most of censoring (due to administrative censoring) is non-informative censoring, or independent censoring.

Poisson regression

A Poisson regression model allows us to quantify the incidence density (# of events/person time at risk) as a function of many exposures and covariates.

The Poisson regression model can be represented as

$$\lambda_k = \exp\left(\alpha + \beta X + \gamma \mathbf{Z}\right) \text{ or } \log \lambda_k = \alpha + \beta X + \gamma \mathbf{Z}$$

where index k = 1, 2, …, K levels of the joint exposure X and covariate vector Z.. The intercept coefficient α (with log y accounted for) is the incidence density for the group defined by a value of zero on the exposure and covariate vector. The coefficient vector γ are the log incidence density ratios for unit changes in the

respective components of covariate vector Z, holding exposure (and other components of Z) constant at any level. Incidence density (rate) of HF in various strata was estimated assuming a Poisson distribution.

Hazards and Cox regression model

Hazard is defined as instantaneous risk at a given time. It can be represented as probability of event in a small interval. Usually it is estimated at each event. $h(t) = \lim_{\Delta t \to 0} \Pr(t < T \le t + \Delta t \mid W < t \le T)/\Delta t$.

The Cox proportional hazards model can be represented as

$$h(t) = h_0(t) \times \exp(\beta X + \gamma \mathbf{Z}),$$

where $h_0(t)$ is the reference hazard function for those with $X = \mathbf{Z} = 0$ and is sometimes called the baseline hazard function. Cox proportional hazards model is semi-parametric and doesn't has an intercept coefficient. In this model β coefficient is the log of hazard ratio per unit change in exposure X while holding other variables constant at any level and γ is the vectors of log hazard ratios for unit changes in the components of $\mathbf{Z}$ holding the exposure and other components of $\mathbf{Z}$ constant at any level. The baseline function can take any shape the shape of the hazard function over time). Another assumption is that the hazard ratio remains constant during the study follow up i.e. hazards are proportional. Compliance with the proportional hazards assumption was examined for the main exposure using log – log curves and no obvious violation was seen for FEV1 or FVC quartiles.

The variables included in the above two studies are shown in Table 7. We will examine the incidence density of HF over the course of follow up assuming both a Poisson or a negative binomial distribution of events for each race and sex groups.

Cox regression models were used to assess the relationship between race and gender specific quartiles of FEV1 (and FVC), and airflow obstruction with incident HF for each race and gender group.

All Cox models were adjusted for age, height, and squared height (height2) since use of percent predicted lung function(s) can violate the assumptions of homogeneity of variance required to interpret the estimates correctly and has been discouraged, in favor of adjustment using height and height2 (22). The potentially strong confounding due to cigarette smoking was addressed by stratified analysis by smoking for each race and gender group. Further, models were adjusted for prevalent CHD and its traditional risk factors. As chronic inflammation may be an intermediary for this association, a change in the magnitude of the estimates after additional adjustment for pro-inflammatory, pro-coagulability markers and obesity was evaluated. Lastly, adjustment for maximum inspiratory pressure was done to adjust for overall decreased muscle strength.

Multivariable adjusted cumulative failure estimates were plotted by quartiles of FEV1, as the inverse of the survival function (1-S (t+0)) to yield the estimated cumulative proportion of those who developed heart failure at any time point t.

Compliance with the proportional hazards assumption was examined for the main exposure using log – log curves and no obvious violation was seen for FEV1 or FVC quartiles.

Analysis for Paper II

<u>Risk scores</u>

A risk score Z=XBETA could be obtained for each individual in a sample by summing the products of regression beta coefficient from a Cox Proportional Hazards model regression and individual's value for that particular variable. The beta coefficient can be derived from either an external sample or derived from the study sample itself.

i.e. Z_i = Sum ($X_{ai}{}' \beta_a$), Z_i = risk score for ith individual, $\mathbf{Xai}$ is the value of Xa risk factor for ith individual and β is regression coefficient for the Xa variable from the multivariable model.

<u>Discrimination</u> The primary concern of a risk score is its ability to discriminate between those who had event from those who did not. A simple measure of this

property is the proportion of HF cases in the highest decile of predicted risk, or the ratio of cases in the highest decile to lowest decile or lowest quintile of predicted risk. Other commonly used approaches are based on the change in area under the curve (AUC) of a ROC curve, or its proxy the c-index for classification(Harrell, Lee et al. 1996) as an estimate of the probability that a model assigns a higher risk to those who develop HF within the follow-up period compared to those who do not. Since closely related, the c-index has limitations similar to those of the ROC curves (Graf, Schmoor et al. 1999; Pencina, D' Agostino RB et al. 2008). Among these statistics, AUC is more commonly used and understood statistics to examine and compare the discrimination of the models.

By taking censoring into consideration, AUC in the context of long term risk prediction can be defined as the probability that a person with disease onset by time T_0 has a higher risk score than a person with no event by time T_0, $P(Z_i > Z_j \mid D_i(t) = 1 \,\&\, D_j(t) = 0)$ where D(t) is an indicator variable for event or no event by time t, and Z denotes risk score.[3] It is important to restrict to only those events occurring at time $\leq T_0$ as estimations below are based on a fitted survival function. Chambless, Diao et al provided an estimator of AUC which was a function of time, thus accounted for censoring. Current work based on Gang, Chambless et al further modifies extended AUC as probability of one person with earlier disease onset by time T_0 having higher score than another person with later disease onset, $P(Z_i > Z_j \mid T_i < T_j \text{ I } T_i < T_0)$.

AUC is the full area estimated giving equal weights to all false positive rates. This does not take into account the shape of the ROC curve and thus neglects the clinical need of knowing the partial AUC under low false positive rates (such as 0-0.2)(McClish 1989). Other measures of separation like PSEP (prognostic separation) i.e. predicted probability of HF for the group with worst risk score – predicted probability of HF for the group with best risk score(Altman and Royston 2000), and SEP (separation) i.e., weighted geometric mean of absolute relative risk between a strata and baseline have been described (Sauerbrei, Hubner et al. 1997).

In this study we will focus on AUC and novel method as described below. Other recent developments consider the net reclassification improvement for meaningful cut-offs and integrated discrimination improvement if no risk cut-off for decision making exists (Pencina, D' Agostino RB et al. 2008; Pepe, Feng et al. 2008). These methods seem more meaningful for clinical decision making than c-statistics and also provide much greater power to test incremental values(Pencina, D' Agostino RB et al. 2008).

The NRI statistics cross tabulate number of individuals classified into various risk levels like low, medium, and high by a basic model and another full model. The movement of individual from a category of basic model to a new category could be upward, downward, or no movement. Based on individuals

actual outcome, the full model may be reclassified him/her appropriately (upward movement of someone with event and downward of someone who didn't had event) of inappropriately.

i.e.,

$$\text{Model Improves} = P(Z_{up} | D = 1) + P(Z_{down} | D = 0)$$

$$\text{Model Worsens} = P(Z_{up} | D = 0) + P(Z_{down} | D = 1)$$

Table 6. Reclassification of individuals into risk categories by an extended model and appropriateness of such reclassification (Adapted from master's paper of Mr. Cui Gang, Biostatistics, UNC, Chapel Hill		Extended (Full) Model		
		Low Risk	Medium Risk	High Risk
Basic Model	**Low Risk**	Neither	UP Improve if D=1 Worsen if D=0	UP Improve if D=1 Worsen if D=0
	Medium Risk	DOWN Worsen if D=1 Improve if D=0	Neither	UP Improve if D=1 Worsen if D=0
	High Risk	DOWN Worsen if D=1 Improve if D=0	DOWN Worsen if D=1 Improve if D=0	Neither

The NRI can thus be defined as the probability the full model improves the overall risk prediction minus the probability the full model worsens the overall risk prediction.

$$NRI = [P(Z_{up} | D = 1) + P(Z_{down} | D = 0)] - [P(Z_{up} | D = 0) + P(Z_{down} | D = 1)]$$

Calibration To check for goodness of fit to the data comparisons will be made at two levels. First, for combinations of predictor variables we will use Hosmer and Lemeshow's delta-chi square influence statistic (the decrease in the Pearson goodness of fit statistic that results from deleting the set of observations that share a specific covariate pattern) and the Pregibon delta-beta statistic, which results from the Pearson residual and the "hat matrix" (Hosmer and Lemeshow 1999). Second, the overall function's predicted risks will be used to divide the observations into deciles of predicted, compared to observed risk. Plots will be constructed showing predicted and actual event rates for each decile (Arjas plots) (Gronnesby and Borgan 1996).

The Gronnesby and Borgan statistic (GB-stat) as proposed by Gronnesby and Borgan (1996) is a goodness of fit test for the Cox proportional hazard model. By computing the martingale residuals for each decile, the GB-stat tests the hypothesis that the expected value of the sum of these residuals is equal to zero.

Correction for Optimism in estimate

It is expected that AUC statistics calculated using risk score with beta estimates derived from same sample will behave better than AUC derived in an external sample. We will use bootstrapping (Harrell, Lee et al. 1996), re-sampling from the study sample with replacement, to correct for some of this optimism. We

will do 1000 bootstraps using the study sample size. Bootstrapping provides stable estimates with lower bias as compared to the other similar methods for validation including split-sample, cross-validation (Steyerberg, Harrell et al. 2001) and permits using the entire dataset as well as allowing for estimation of the error rates or for the reduction of bias of effect estimates. The bias-corrected coefficients will be used for comparisons of the estimates. The average optimism i.e., (measure $_{bootstrap\ samples}$ − measure $_{original\ dataset}$) will be subtracted from the original performance measure to provide a more realistic estimate.

J. Methodological strengths and limitations

4.6.1 Strengths The ability to use extant data from a large, population-based biracial closed cohort with an average of 10 years of follow up provides excellent opportunity to address a novel study question with a clear translation potential. The availability in this cohort of modern biomarkers related to HF and of application in clinical practice and epidemiologic research represents a particular strength. The disciplined plan of analyses and methodological rigor contributed by the newer analytic and validation tools built into this proposal provide a better-than-usual assurance against particularistic associations or over-fitting due to sparse outcomes (Harrell, Lee et al. 1985). This study will provide a much useful external validation to Health ABC study using similar criteria to ascertain outcome. For the incremental value of biomarkers, while the study results would be internally valid and corrected for optimism replication in other settings and populations will be needed.

4.6.2 Limitations   Our outcome is incident hospitalized HF, which represents an advanced stage of HF requiring hospital admission. Also, these events are not validated and rely on ICD codes primary meant for administrative purposes. This may be acceptable as the purpose of the study is to aid in the identification of individuals at risk at an early stage of the natural history of HF, allowing timely diagnosis and proactive management. As there are no set criteria for hospitalization of patients presenting with symptoms of HF, the set of variables identified may have some restrictions to its generalizability.

As a further limitation it should be mentioned that information on cardiac imaging is not available for a large proportion of cohort, hence type of ventricular dysfunction i.e., systolic vs. diastolic is unknown. It should be noted however that however that there is little known difference in the signs and symptoms of systolic and diastolic HF, leading to our expectation that no appreciable loss of discriminatory information will occur in the absence of data on cardiac imaging. Since the primary purpose of the HF risk prediction function is to aid in the early identification of individuals at risk of HF in primary care settings, recourse to cardiac imaging for such a purpose would not be desirable.   Instead, the penetration of biomarkers into clinical practice poses the question of their putative usefulness in predicting HF risk if considered in the context of "established" HF risk prediction equations and the use of simple measures commonly used in clinical practice. Lastly, it must be noted that the ARIC cohort

does not include Hispanics or Indian Americans in numbers sufficient to perform

analyses in these groups.

Chapter IV

RESULTS

A. Manuscript 1: Obstructive airway disease, lung function and Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) Study
1. Introduction

Heart Failure (HF) is a major cause of disability and premature mortality in the U.S. (Rosamond, Flegal et al. 2008). It has a poor prognosis (Levy, Kenchaiah et al. 2002), and the cost associated with its treatment exceeds those for coronary artery disease and cancer combined, accounting for about 5.4% of the total U.S. health care cost (O'Connell and Bristow 1994). Chronic obstructive pulmonary disease (COPD) remains the fourth leading cause of morbidity and mortality in the U.S. and it is projected to surpass stroke as the third leading cause of deaths by 2020 (Jemal, Ward et al. 2005). The estimated direct and indirect cost of COPD is $24 billion (1997) in the U.S. (Pauwels, Buist et al. 2001).

COPD is a common comorbidity among patients with HF, and vice versa (Dahlstrom 2005; Rutten, Cramer et al. 2006; Iversen, Kjaergaard et al. 2008), (Rutten, Cramer et al. 2005). A large body of literature suggests higher cardiovascular mortality in individuals with COPD and low lung volume (Pauwels,

Buist et al. 2001; Sin, Wu et al. 2005; Mannino, Doherty et al. 2006; McGarvey, John et al. 2007). An overlap of HF and COPD has been alluded to in the literature. In patients with COPD the predicted percentage of FEV1 was inversely associated with left ventricular ejection fraction(Yilmaz, Gencer et al. 2005) and especially severe COPD causes right sided HF or cor-pulmonale (Budev, Arroliga et al. 2003) and impaired left ventricular filling (Boussuges, Pinet et al. 2000; Yilmaz, Gencer et al. 2005; Funk, Lang et al. 2008). Recent studies suggests that left ventricular diastolic and systolic dysfunction is frequently seen in mild COPD (Sabit, Bolton et al. 2007), but few studies have examined sub-clinical or spirometry-based airflow obstruction and incident HF.

To our knowledge there are no population-based reports that systematically examine COPD and the risk of incident HF; similarly, little information is available on the relationship between pulmonary function and incident HF. We hypothesized that low lung function as well as airflow obstruction in individuals without HF is associated with increased risk of subsequent HF, and that this relationship would be consistent across groups defined by race, gender, and smoking status. We addressed these questions in a large biracial cohort of men and women in four U.S. communities.

2. Methods

Study population

The ARIC Study enrolled 15,792 men and women ages 45-64 years sampled from four U.S. communities: Forsyth County, NC; Jackson, MS; seven northwestern suburbs of Minneapolis, MN; and Washington County, MD. Enrollment at the Jackson, MS site was restricted to black residents, while black residents were over-sampled in Forsyth County. Baseline examinations of the cohort were conducted from 1987 to 1989 to collect standardized information on socioeconomic indicators, medical history, family history, cardiovascular risk factors, serum chemistries, electrocardiograms (ECGs), medication use, and lung volumes. Three re-examinations followed the baseline visit, as well as annual telephone interviews and active surveillance of hospitalizations and death.

Those with prevalent HF (n=775) or missing (n=325) data on HF at baseline (Loehr, Rosamond et al. 2008) ; missing (n=127) or implausible (n=12) lung volume data; missing information on important covariates (n=780); race other than black or white (n=48) were excluded from these analyses. The final study sample was 13,660.

Exposure

Pulmonary function was assessed at the baseline visit (1987-89) using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Inc.) and Pulmo-Screen II software (PDS Healthcare Products,496 Inc.).

Spirometry was conducted using American Thoracic Society (ATS) guidelines (1987). From at least three acceptable readings, of which at least two were reproducible (volumes within ± 5%), a best reading was selected by computer software and confirmed by technician using ATS criteria for acceptability. The protocol was standardized across four field centers, with training and certification of pulmonary technicians and extensive quality assurance throughout the study. History of respiratory illness was obtained via standardized questionnaire by trained personnel (Ferris 1978). Chronic bronchitis was defined as productive cough for at least 3 months in 2 contiguous years. History of respiratory illness was determined by asking participants if they were ever diagnosed with bronchitis/emphysema/asthma and whether it was confirmed by a doctor. COPD was defined by a positive response to either a physician diagnosis of emphysema or bronchitis. Also, a FEV1/FVC ratio of less than 0.7 was used to define possible obstructive respiratory illness. Those with possible obstructive disease by spirometry were further divided into mild (FEV1 ≥ 80% of predicted value) and moderate/severe (FEV1 < 80% of predicted) (1995; Pauwels, Buist et al. 2001).

Covariates

At baseline, prevalent coronary heart disease (CHD) was ascertained by self-report and a 12-lead ECG. Hypertension was defined by diastolic pressure≥ 90 mm Hg or systolic pressure≥140 mm Hg on the average of the last 2 of 3 measurements, or the use of anti-hypertensive medications. Diabetes was defined by the presence of serum glucose level >= 200 mg/dl, an 8-hour fasting

glucose level >=126 mg/dl, a self-reported history of physician-diagnosed diabetes, or the current use of hypo/antihyper-glycemic medications. Other medications intake including beta blockers was self-reported or derived from medicines brought by participants during exam. Cigarette smoking status was defined as currently smoking or a history of ever smoking four hundred cigarettes or more. The average number of cigarettes/day and number of years of smoking reported were multiplied to derive cigarette-years of smoking. Body mass index was defined as the ratio of measured weight (kilograms) and measured height2 (in meters2). Participants identified themselves as belonging to American/Alaskan Indian, Asian, black, or white race.

Heart Failure

Incident HF was defined as the first HF hospitalization with an HF discharge code or HF as the underlying cause of death on a death certificate (n=84). Hospital discharge diagnoses were coded using the International Classification of Diseases Code, Ninth Revision (ICD-9, code 428), and deaths were coded using ICD-9 or ICD-10 (codes 428 and I 50, respectively). Cohort follow up for the current analysis ended on 31st December 2004.

Statistical Methods

Means (standard deviations) and proportions of characteristics at baseline and follow up HF event rates were calculated for quartiles of FEV1. A higher proportion of blacks and women were in the lower quartiles of FEV1 and FVC; thus all analysis (except for table 7) used race and gender specific quartiles of

FEV1. Incidence density (rate) of HF in various strata was estimated assuming a Poisson distribution. Cox regression models were used to assess the relationship between race and gender specific quartiles of FEV1 (and FVC), and airflow obstruction with incident HF for each race and gender group.

All Cox models were adjusted for age, height, and squared height (height2) since use of percent predicted lung function(s) can violate the assumptions of homogeneity of variance required to interpret the estimates correctly and has been discouraged, in favor of adjustment using height and height2 (Vollmer, Johnson et al. 1987). The potentially strong confounding due to cigarette smoking was addressed by stratified analysis by smoking for each race and gender group. Further, models were adjusted for prevalent CHD and its traditional risk factors. As chronic inflammation may be an intermediary for this association, a change in the magnitude of the estimates after additional adjustment for pro-inflammatory, pro-coagulability markers and obesity was evaluated. Lastly, adjustment for maximum inspiratory pressure was done to adjust for overall decreased muscle strength.

Multivariable adjusted cumulative failure estimates were plotted by quartiles of FEV1, as the inverse of the survival function (1-S (t+0)) to yield the estimated cumulative proportion of those who developed heart failure at any time point t. To evaluate the potential influence of a misdiagnosis of incident HF on studied association, additional sensitivity analysis were done, (a) by excluding

those with baseline COPD, CHD, or both and (b) by censoring HF events with a concomitant discharge code for acute exacerbation of COPD, respiratory failure, or both. Detailed methods and results of the sensitivity analysis are reported in the footnote to online Supplemental Table 7. Compliance with the proportional hazards assumption was examined for the main exposure using log – log curves and no obvious violation was seen for FEV1 or FVC quartiles. SAS, version-9.1 and STATA-IC, version-10 software were used for analysis. A $p < 0.05$ for a two-sided test was considered statistically significant.

Results

A total of 1369 (10%) participants developed HF over the average follow-up of 14.9 years. Characteristics of all study participants by decreasing gender-specific quartiles of FEV1 are shown in Table 7. At study baseline, those in the lower quartiles of FEV1 had a higher mean age, cigarette-years of smoking, systolic blood pressure, markers of inflammation, a lower height, and a higher proportion were current smokers, black, women, or had respiratory illness. The 25th, 50th, and 75th percentiles of FEV1 in liters were 1.9, 2.2 and 2.5 in black females; 2.6, 3.0, and 3.4 in black males; 2.2, 2.5, and 2.8 in white females; 3.0, 3.5, and 3.9 in white males.

A monotonic increase in the rate of incident HF with decreasing quartile of FEV1 was seen in both blacks and whites, after adjusting for age, and height (Figure 1). The age and height adjusted average incidence rates of HF per 1000

person year by quartiles of FEV1 were – from highest to lowest quartile – 14.7 ,

8.2, 5.1, and 2.9 for blacks, and 11.8, 6.6, 4.1, and 2.3 for whites.

In Cox regression models adjusted for age, smoking, and height, the

hazard ratios (HRs) of HF increased monotonically and inversely by quartiles of

FEV1, for both genders in each race group (Figure 2). The age and height

adjusted HRs and their 95% confidence interval (95%CI) contrasting those in the

lowest quartile of FEV1 to those in highest for HF were 3.48 (2.24, 5.40) among

black female, 2.88 (1.80, 4.61) among black males, 6.95 (4.42, 10.94) among

white female, and 5.66 (4.04, 7.91) among white males. The HRs comparing the

highest to lowest quartile were of greater magnitude in whites than in blacks, and

in women than in men, and were statistically significant for all contrasts to the

highest quartile except for third quartile among black males. In similar models,

HR estimates were slightly higher when contrasting quartiles of FVC (data not

shown) than FEV1.

The above associations were observed across all smoking status

categories. Among never smokers, the age, height, height2 adjusted HF hazard

rate estimate was about 2.5 to 3 times higher those in the lowest quartile of FEV1

than in the highest (Table 8).

In multivariable models adjusted for age, height, prevalent CHD, and

traditional cardiovascular risk factors the HRs (95% CI) contrasting the lowest

with the highest quartiles of FEV1 were 2.91 (2.14, 3.97) for women and 2.23 (1.69, 2.93) for women (Table 8). On further adjustment for covariates including prevalent CHD and traditional cardiovascular risk factors, body mass index, white blood cell count, fibrinogen, Von-Willebrand's factor and serum albumin, the magnitude of the hazard ratios were attenuated slightly, although they remained statistically significant for all race and gender group (Table 8). The multivariable adjusted cumulative risk of incident HF by quartiles of FEV1 is shown in Figure 3. They show a graded increase in the risk of HF for decreasing quartiles of FEV1 throughout the study period.

In multivariable adjusted models, the hazard ratios for HF contrasting those with FEV1/FVC <70% to those with ≥70% were 1.44 (1.20, 1.74) and 1.40 (1.13, 1.72) for women and men, respectively (Table 9). Of note, the severity of COPD was predictive as spirometry-defined mild COPD was not associated with incident HF. On testing associations of several definitions of respiratory illness with incident HF, a self-reported physician diagnosis of emphysema had the strongest association with incident HF in both men and women, whereas self-reported physician diagnosis of asthma had a weak association in women, and no association in men (Table 9). Self-reported COPD was similar to spirometry-defined COPD in its association with incident HF. For example, the HR (95% CI) comparing those with a self reported diagnosis of COPD than those without were 1.84 (1.47, 2.31) for women and 1.44 (1.08, 1.91) for men.

Discussion

We observed a strong inverse association between baseline lung function with incident HF, and a monotonic, direct association between airflow obstruction and incident HF. These associations were seen across groups defined by race, gender, and smoking status. Notably, the relationship was seen in never-smokers and after adjustment for smoking status and cigarette-years of smoking, indicating that our results are not primarily confounded by smoking.

These results in a population-based cohort are consistent with clinical observations, but also with two prior reports from population based cohorts, indicating that a low FEV1 was strongly predictive of HF, independent of many traditional and non-traditional risk markers (Eriksson, Svardsudd et al. 1989; Gottdiener, Arnold et al. 2000). The present study extends these results by the length and completeness of its follow-up, a replication in African Americans, and by examination of markers of chronic inflammation a potential mechanism,.

We also found a consistent association of interviewer-ascertained chronic bronchitis, self reported COPD and emphysema, and airway obstruction (FEV1/FVC<70%) with incident HF, but not with asthma. The weak but statistically significant association of asthma with incident HF among women could be explained by misdiagnosis of COPD for asthma in primary care, reportedly more common in women than in men (Chapman, Tashkin et al. 2001). Our results are similar to those of a large retrospective case control study based

on claims data, where COPD was associated with an almost threefold higher rate of HF hospitalization (Sidney, Sorel et al. 2005), although the magnitude of that association was of considerably greater magnitude than seen in this study. Rates of heart failure and other CVD related hospitalizations were also reported to be higher in those with COPD as compared to the general population of Canada (Huiart, Ernst et al. 2005). Further, these associations were seen with moderate/severe COPD (defined with spirometry) and not with mild disease. The only other population based study to examine the association of low FEV1/FVC (<60% vs. higher) with HF events did not find an association (Kannel, Seidman et al. 1974), although limited statistical power is a likely explanation for the observed lack of effect.

Several traditional cardiovascular risk factors are associated with both low lung function and HF, and thus could confound the associations reported here. Both FVC and FEV1 show an inverse association with blood sugar, blood pressure, serum cholesterol, BMI and left ventricular mass(Kannel, Hubert et al. 1983; Enright, Kronmal et al. 1995; Enright, McClelland et al. 2001; Gunnell, Whitley et al. 2003). Our estimates were somewhat attenuated after adjustment for these putative confounding variables, but they remained statistically significant (Table 8-9). It has been reported that lower lung volumes may be seen in HF patients with large heart size due to lung impingement(Agostoni, Cattadori et al. 2000; Olson, Beck et al. 2006). This is unlikely to be common in a population sample of middle-aged individuals without HF at study baseline;

moreover, statistical adjustment for left ventricular mass estimated by the Cornell voltage did not change the magnitude of our estimates. Overweight and obesity were considered as possible confounders. However, no clear patterns of association between ponderosity and lung function or respiratory disease were seen in these data however, and statistical adjustment for BMI did not change our results appreciably.

Levels of systemic markers of inflammation are higher in those with low lung volumes, and links between inflammation and HF have been proposed (Gunnell, Whitley et al. 2003; Barnes 2007). These high levels may reflect either spill of inflammatory markers from inflammation localized to the lungs or an upstream up-regulation of inflammatory cascade. (Barnes and Celli 2009). We observed some attenuation of the HR estimates in our study after adjustment for baseline levels of inflammatory makers, which lends some support to the inflammation-HF hypothesis. Beyond those observed in cigarette smokers, declines in lung volumes may also be seen with a higher exposure to road traffic (Kan, Heiss et al. 2008) with and diabetes (Yeh, Punjabi et al. 2008). However, it is far from established whether the risk of HF is influenced by the latter two characteristics. Exercise training appears to improve physical function in both COPD and HF – primarily by improving skeletal muscle function – but possibly by reducing inflammation as well (Coats 1999; Celli and MacNee 2004). Whether it can prevent HF in COPD patients needs evaluation.

Kannel et al. suggested that decreased muscle strength may partially account for the inverse association of FEV1 with HF (Kannel, Seidman et al. 1974). Statistical adjustment for maximum inspiratory pressure, a measure of respiratory muscle strength, indeed attenuated the magnitude of our results. For reasons that are not obvious this attenuation was of greater magnitude in the black members of the ARIC cohort. We also examined the potential confounding bias introduced by the use of beta blockers but did not see evidence of confounding (data not shown).

Some of the traits mentioned above as covariates and potential intermediaries may be associated with HF directly or indirectly through their association with CHD. For instance, low FVC is associated with incident diabetes(Yeh, Punjabi et al. 2005), sub-clinical atherosclerosis (Schroeder, Welch et al. 2005), arterial stiffness (Bolton, Cockcroft et al. 2009), and incident ischemic heart disease (Cook and Shaper 1988; Marcus, Curb et al. 1989; Engstrom, Lind et al. 2002; Schroeder, Welch et al. 2003). Empirically, excluding those with prevalent CHD at baseline did not visibly change the results (Table 10).

Misclassification of hospitalized COPD exacerbations as HF is conceivable given the many overlapping signs and symptoms(Hawkins, Petrie et al. 2009), and that the HF events in this study were not validated by chart review. An ICD code- 428.x has a positive predictive value of 94.3% when compared to

Framingham criteria (Lee, Donovan et al. 2005), and 83.0% compared to a physician diagnosis and pulmonary edema on chest X-ray(Goff, Pandey et al. 2000).To evaluate whether our findings may be a result of misclassification of incident HF sensitivity analyses were conducted as stated in the methods section. The estimated associations didn't change appreciably following exclusion of COPD at baseline, or by censoring those with concurrent COPD and HF (Table 10). Lastly, a decreased lung function may contribute to early exacerbation of asymptomatic ventricular dysfunction and possibly to lead-time bias. Given the strength of the estimates observed and the almost constant hazard ratio estimates over time, if present these biases are unlikely to have an effect that would alter the inferences presented here.

Several limitations of this study should be mentioned. The most important among them is the lack of validation and detailed characterization of the heart failure events. Further, respiratory symptoms and diagnoses were self reported and not validated. Perhaps less worrisome, smoking status was self reported and not validated with biomarkers, thus some residual confounding due to smoking could not be ruled out, and neither post bronchodilator lung function or total lung volume were measured. Lastly, although adjustment for BMI did not influence the estimates, residual confounding due to sleep apnea could not be ruled out. The strengths of our findings include their prospective and population-based nature, their internal consistency including among non-smokers, the

sizeable magnitude of hazard ratio estimates even after multivariable adjustment, and the imperviousness of the results to various sensitivity analyses.

Studies are needed that can address the associations reported here with further characterization of HF into systolic and diastolic phenotypes. Whether improvement (or a slower decline) in lung function with smoking cessation(Scanlon, Connett et al. 2000), increased physical activity(Garcia-Aymerich, Lange et al. 2007) or other novel interventions is related to future risk of HF similarly need attention. In a population based study, CT scan-defined emphysema, and spirometry-defined airflow obstruction were linearly associated with impaired ventricular filling, and reduced cardiac output but not with ejection fraction (*Barr et al, Left ventricular filling in emphysema and airflow obstruction; unpublished*). A recently reported large burden on unrecognized heart failure in patients with COPD (Rutten, Cramer et al. 2005) further suggests that more attention to HF in individuals with COPD is warranted. An enhanced understanding of the pathophysiologic changes in heart structure and function in the context of COPD would be similarly important.

An increase in pulmonary vascular resistance, pulmonary artery pressure, lower pulmonary vessel endothelial function, and endothelial proliferation in pulmonary vasculature is seen with alveolar hypoxia and in individuals with even mild/moderate COPD (Santos, Peinado et al. 2002; Santos, Peinado et al. 2003; Budhiraja, Tuder et al. 2004; Han, McLaughlin et al. 2007; Barnes and Celli

2009). It seems reasonable to think that such changes may manifest in early right ventricular structural (Vonk-Noordegraaf, Marcus et al. 2005) and functional abnormalities that could ultimately lead to a deterioration of left ventricular function and clinical HF due to inter-ventricular dependence (Vonk Noordegraaf, Marcus et al. 1997). Several other systemic mechanisms such as systemic inflammation (Schroeder, Welch et al. 2003), autonomic dysfunction (Undem and Kollarik 2005), oxidative stress (Mannino, Doherty et al. 2006), chronic muscle wasting (Barnes and Celli 2009) have been implicated to result in new-onset HF in individuals with COPD. Further, animal studies show an increased right sided heart injury with increased end expiratory volume as seen in acute exacerbation of COPD (Simpson, Brunt et al. 2009).

In conclusion, in this large population based closed cohort study with long term follow up, we observe that low FEV1, low FVC, self reported COPD, and airway obstruction are associated with incident HF.

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Table 7. Characteristics of study participants at baseline and incident heart failure across quartiles of FEV1 (N=13360)								

	FEV1 quartile at baseline†							
	Q1(0.5 - 2.3 L)		Q2 (2.3 – 2.8 L)		Q3(2.8 - 3.3 L)		Q4 (3.3 - 5.9 L)	
Characteristic*	n=3415		n=3415		n=3415		n=3415	
Demographic/Lifestyle/Clinical								
Age (in years)	56.06	5.61	54.15	5.7	53.45	5.73	52.62	5.4
Male	14.6		21.5		51.2		93.3	
African American	39.1		27.2		20.6		11.6	
Hypertension	41.8		31.7		29.7		23.5	
Diabetes	15.1		9.6		9.4		7.4	
Current smoker	36.5		25.3		21.6		17.7	
Former Smoker	21.3		26.6		34.7		44.8	
Cigarette-years of smoking	361.6	467.9	269.0	397.5	305.6	434.5	307.9	386.3
Usual ethanol intake (in grams/week)	27.9	82.3	31.2	75.6	49.1	107.1	62.6	106.3
Height (in centimeters)	161.9	7.5	164.8	7.1	169.9	7.3	177.6	6.5
Systolic blood pressure (in mm of Hg)	124.9	20.4	120.1	18.4	119.4	18.1	118.4	15.6
Diastolic blood pressure (in mm of Hg)	73.2	11.8	72.6	10.9	73.5	11.0	74.4	10.3
LDL cholesterol (in mg/dL)	139.4	42.0	136.2	38.4	136.3	38.8	138.2	36.6
HDL cholesterol (in mg/dL)	55.4	17.7	55.4	16.9	52.2	17.4	45.5	13.8
Body Mass Index (in kg/meter^2)	28.2	6.4	27.4	5.5	27.1	4.9	27.2	3.7
Inflammatory Markers								
White blood count (x 10^3/mm^3)	6.4	2.1	6.0	1.9	6.0	1.8	5.9	2.1
Fibrinogen (mg/dl)	322.4	71.0	302.0	61.3	297.0	61.6	284.5	55.9
Albumin (in g/dL)	3.2	0.7	3.2	0.6	3.1	0.6	3.1	0.6
Von-Willebrand's Factor (%)	126.1	53.2	117.1	46.6	114.1	44.2	110.0	42.6
Study Exposure(S)								
Forced Expiratory Volume (1s, in L)	1.9	0.3	2.5	0.1	3.0	0.2	3.9	0.4
Forced Vital Capacity (in Liters)	2.8	0.5	3.4	0.4	4.0	0.4	5.1	0.6
FEV(1)/FVC	70.8	11.0	75.1	6.8	75.6	6.4	76.3	5.4
FEV1/FVC <70%	41.1		22.5		20.6		15.8	
Chronic bronchitis¶	7.6		4.1		4.3		3.8	
Self reported diagnosis of bronchitis	13.3		6.9		5.3		3.7	
Self reported diagnosis of emphysema	3.7		0.9		0.8		0.7	
Self reported diagnosis of COPD‖	15.4		7.5		5.9		4.3	
Self reported diagnosis of asthma	8.5		4.3		4.2		3.5	
Follow up								
Heart Failure events	16.2		9.3		8.3		6.3	

Follow up duration (in years)	14.0	4.3	15.1	3.4	15.1	3.3	15.4	3.0
Heart failure rate/1000 person years	11.5		6.1		5.5		4.1	

*Expressed as Mean and Standard deviation (SD) or Percentages

FEV1 = Forced Expiratory Volume during 1st second measured using standardized spirometry at study baseline. Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004.

¶Chronic bronchitis was defined as productive cough for at least 3 months in 2 contiguous years;

‖Self-reported diagnosis of Chronic Obstructive Pulmonary Disease (COPD) is presence of either self reported diagnosis of bronchitis or emphysema.

Table 8. Hazard ratios of HF contrasting the lowest and highest quartiles of FEV1 by incremental level of covariate adjustments (N = 13360)

Gender	Smoking status/ Model	White participants (N = 10293, n = 927) HR (95% CI)			Black participants (N=3367, n = 442) HR (95% CI)			All Participants (N=13360, n=1369) HR (95% CI)	
Women	**Current***	9.87	(3.01,	32.34)	3.56	(1.50,	8.49)	**4.94**	**(2.50, 9.76)**
	Former*	4.35	(1.65,	11.50)	2.99	(1.13,	7.80)	**4.27**	**(2.13, 8.53)**
	No*	3.88	(2.03,	7.42)	3.01	(1.63,	5.56)	**4.01**	**(2.57, 6.27)**
	Model 1[†]	4.80	(3.00,	7.68)	2.98	(1.91,	4.66)	**4.12**	**(2.98, 5.70)**
	Model 2[‡]	3.91	(2.40,	6.35)	2.11	(1.33,	3.34)	**2.91**	**(2.14, 3.97)**
	Model 3[§]	3.61	(2.21,	5.88)	2.00	(1.25,	3.19)	**2.44**	**(1.79, 3.34)**
	Model 4[#]	3.44	(2.03,	5.83)	1.61	(0.95,	2.72)	**2.19**	**(1.54, 3.12)**
Men	**Current***	2.51	(1.31,	4.81)	2.71	(1.25,	5.88)	**2.42**	**(1.48, 3.97)**
	Former*	6.72	(4.07,	11.08)	2.91	(1.23,	6.88)	**5.60**	**(3.65, 8.60)**
	No*	3.04	(1.46,	6.31)	2.44	(0.94,	6.33)	**2.94**	**(1.65, 5.22)**
	Model 1[†]	4.11	(2.89,	5.84)	2.55	(1.57,	4.13)	**3.51**	**(2.65, 4.66)**
	Model 2[‡]	3.03	(2.12,	4.33)	2.23	(1.37,	3.59)	**2.23**	**(1.69, 2.93)**
	Model 3[§]	2.98	(2.07,	4.28)	2.11	(1.30,	2.41)	**1.92**	**(1.44, 2.55)**
	Model 4[#]	2.68	(1.83,	3.92)	1.72	(0.96,	3.07)	**1.80**	**(1.32, 2.44)**

N = study sample size, n = incident HF cases; FEV1 = Forced Expiratory Volume (1second)

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004.

FEV1 quartiles were race and gender specific, and the models contained quartiles as indicator variables to estimate the effect size without assuming log-linearity in FEV1 quartiles. Estimates are reported only contrasting the lowest with highest quartile of FEV1.

Each of the hazard ratio (HR) and its 95% confidence interval (95% CI) is from a separate model. For smoking categories, subset analysis was done by running separate models for each smoking stratum for each race and gender. [*] Hazard ratios and 95% confidence interval, adjusted for age, height, height$^{2.}$

Further models with adjustment for incremental level of covariates were

[†]Model 1: In addition to age, height, height*height, this model additionally adjusts for current smoking status by using two binary variables: current smoking, and former smoking, and Cigarette-years of smoking.

[‡]Model 2: In addition to model 1 covariates, this adjusts for prevalent coronary heart disease, diabetes, hypertension, LDL cholesterol and HDL cholesterol.

[§]Model 3: In addition to model 2 covariates, this adjusts for fibrinogen levels, white blood count, Von-Willebrand's factor, and serum albumin and body mass index.

[#]Model 4: In addition to model 3, this adjusts for maximum inspiratory pressure measured during visit 2 (3 years after baseline visit), with fewer observations (Whites n= 9027, Blacks n= 2820)

Table 9. Hazard ratios of HF for airway obstruction, and self reported diagnosis of respiratory illness. (N = 13130)

	Model 1[†]		Model 2[‡]	
Men	HR (95% CI)*		HR (95% CI)*	
COPD vs. no COPD by spirometry	1.61	(1.36, 1.91)	1.44	(1.20, 1.74)
Mild COPD vs. no COPD by spirometry	0.90	(0.69, 1.18)	0.98	(0.74, 1.29)
Moderate/severe COPD vs. no COPD by spirometry	2.30	(1.90, 2.77)	1.83	(1.49, 2.26)
Chronic bronchitis[¶]	2.07	(1.60, 2.69)	1.42	(1.03, 1.98)
Self reported diagnosis of bronchitis	1.65	(1.20, 2.27)	1.44	(1.04, 2.00)
Self reported diagnosis of emphysema	2.22	(1.51, 3.25)	1.85	(1.23, 2.77)
Self reported diagnosis of COPD[‖]	1.70	(1.30, 2.20)	1.44	(1.08, 1.91)
Self reported diagnosis of asthma	1.06	(0.74, 1.51)	1.15	(0.80, 1.64)
Women				
COPD vs. no COPD by spirometry	1.40	(1.15, 1.71)	1.40	(1.13, 1.72)
Mild COPD vs. no COPD by spirometry	0.90	(0.67, 1.20)	1.07	(0.79, 1.45)
Moderate/severe COPD vs. no COPD by spirometry	2.09	(1.65, 2.65)	1.73	(1.34, 2.22)
Chronic bronchitis[¶]	2.11	(1.54, 2.99)	1.74	(1.34, 2.19)
Self reported diagnosis of bronchitis	2.27	(1.83, 2.82)	1.84	(1.84, 5.28)
Self reported diagnosis of emphysema	4.41	(2.72, 7.16)	3.12	(2.11, 5.93)
Self reported diagnosis of COPD[‖]	2.40	(1.94, 2.96)	1.84	(1.47, 2.31)
Self reported diagnosis of asthma	1.60	(1.17, 2.17)	1.56	(1.14, 2.13)

Hazard ratio, CI = Confidence Interval, COPD = Chronic Obstructive Pulmonary Disease,

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates followed through December 31, 2004. Using spirometry, any COPD was defined as FEV1/FVC <70%,   mild COPD was defined as FEV1/FVC (<70%) and FEV ≥ 80% (predicted) and moderate/severe COPD as FEV1/FVC (<70%) and FEV < 80% (predicted), and no COPD as FEV1/FVC ≥ 70%.

[†]Model 1 is adjusted for age and race;

[‡] Model 2 is adjusted for age, smoking status, cigarette-year of smoking, hypertension, diabetes, LDL-c, HDL-c, body mass

[¶]Chronic bronchitis was defined as productive cough for at least 3 months in 2 contiguous years;

[‖]Self-reported diagnosis of Chronic Obstructive Pulmonary Disease (COPD) is presence of either self reported diagnosis of bronchitis or emphysema.
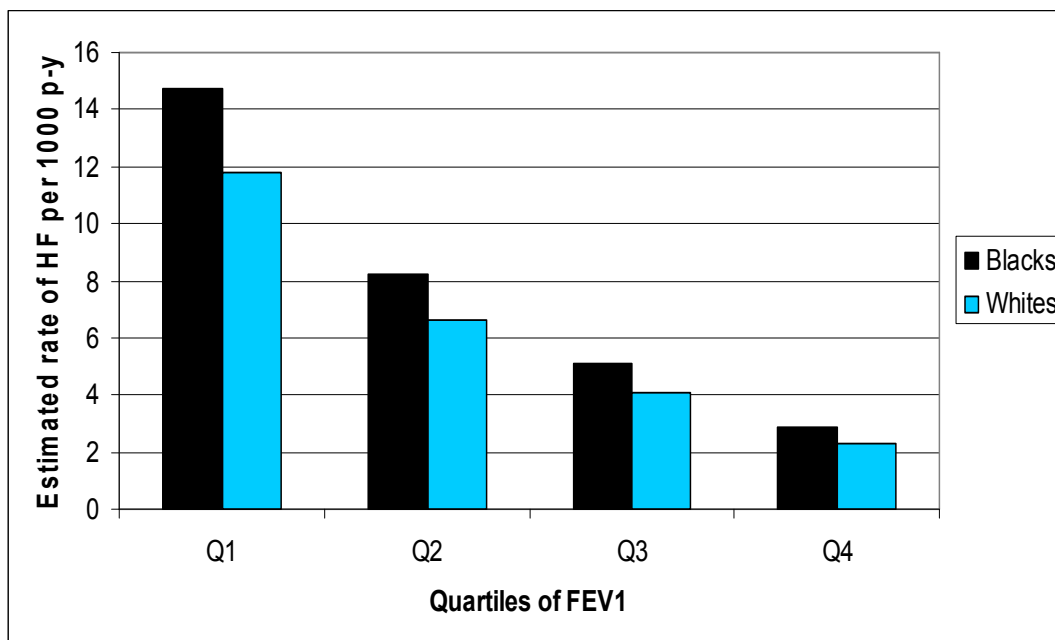
Figure 4. Estimated rate of new-onset heart failure per 1000 person years among black and white cohort members during an average study follow up of 14.9 years by gender and race-specific quartiles of forced expiratory volume, 1s (FEV1). The estimated rates are adjusted for age, height and height*height. The estimated rates shown are for an individual 55 years of age, and 5.5 feet height.

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004. P-Y = person years.

Figure 5. Estimated hazard ratio (95% confidence intervals) of incident heart failure for the quartiles of forced expiratory volume (1s) for each gender and race, adjusted for age, smoking, height, and height*height. Y axis is plotted on a log scale with base 2.

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004.
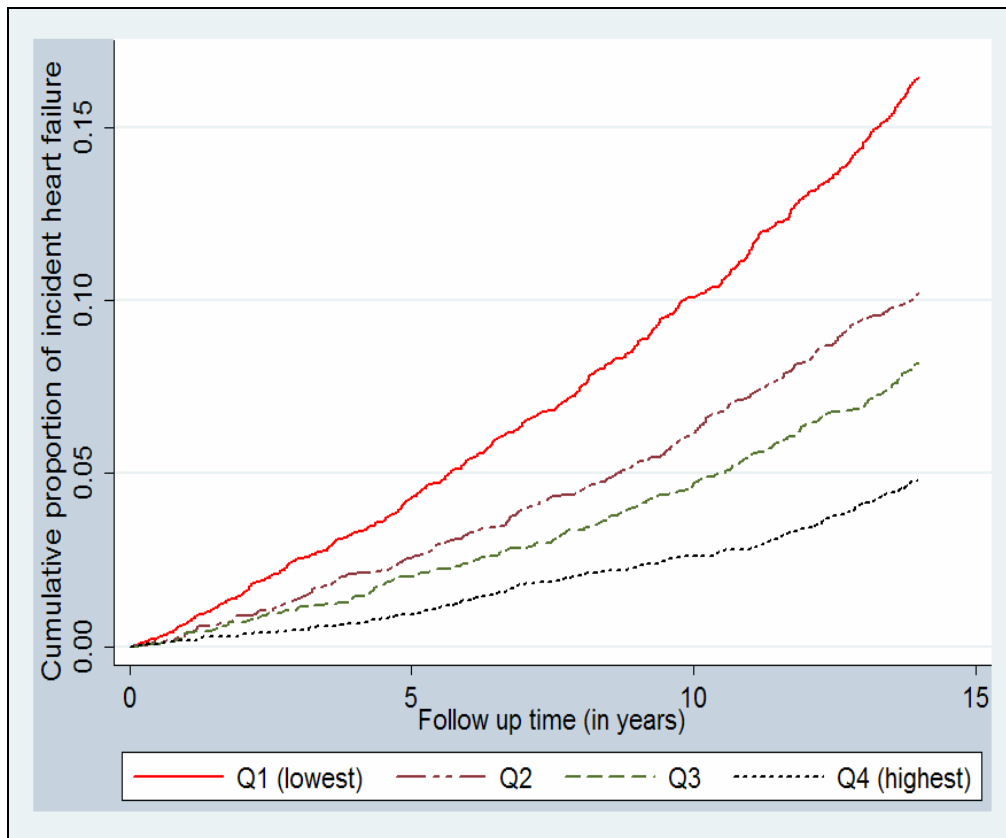
Figure 6. Multivariable adjusted cumulative-events estimates for incident heart failure by quartiles of forced expiratory volume (1s) i.e., Q1 to Q4

Adjusted for age, gender, race, height, height*height, prevalent CHD, diabetes, hypertension, cigarette smoking status, cigarette-years years of smoking, LDL cholesterol, HDL-cholesterol, and body mass index The curves are statistically not similar, using log rank test ($p<0.001$).

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004.

Changes made	Model 1				Model 2			
Table 10. Sensitivity analysis of a ratio estimate for association between FEV1 and incident HF : The ARIC study								
	Female		Male		Female		Male	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
None (copied from Table 8)	4.12	(2.98, 5.70)	3.51	(2.65, 4.66)	2.91	(2.14, 3.97)	2.23	(1.69, 2.93)
Change the baseline cohort								
Exclude participants with self reported COPD	4.00	(2.82, 5.68)	3.29	(2.46, 4.42)	2.92	(2.05, 4.48)	2.48	(1.83, 3.33)
Exclude participants with prevalent CHD	4.04	(2.89, 5.65)	3.06	(2.25, 4.16)	3.07	(2.18, 4.24)	2.63	(1.93, 3.58)
Exclude both baseline COPD & prevalent CHD	3.99	(2.77, 5.69)	2.86	(2.08, 3.95)	2.95	(2.04, 4.27)	2.44	(1.77, 3.37)
Change the outcome definition								
Exclude those with acute exacerbation of COPD (n= 78) during HF hospitalization	3.95	(2.85, 5.48)	3.37	(2.53, 4.51)	2.83	(2.02, 3.96)	2.52	(1.86, 3.83)
Exclude those with acute exacerbation of COPD or respiratory failure (n=229) during HF hospitalization	3.99	(2.82, 5.63)	3.47	(2.55, 4.72)	2.77	(1.95, 3.94)	2.56	(1.87, 3.49)
Censor those with acute exacerbation of COPD or respiratory failure (n=229) during HF hospitalization	3.94	(2.79, 5.56)	3.40	(2.50, 4.62)	2.70	(1.90, 3.84)	2.52	(1.85, 3.44)

Data from the Atherosclerosis Risk in Communities (ARIC) Study baseline examination (1987-89) in a sub-sample without prevalent heart failure and non missing information on important covariates, followed through December 31, 2004.

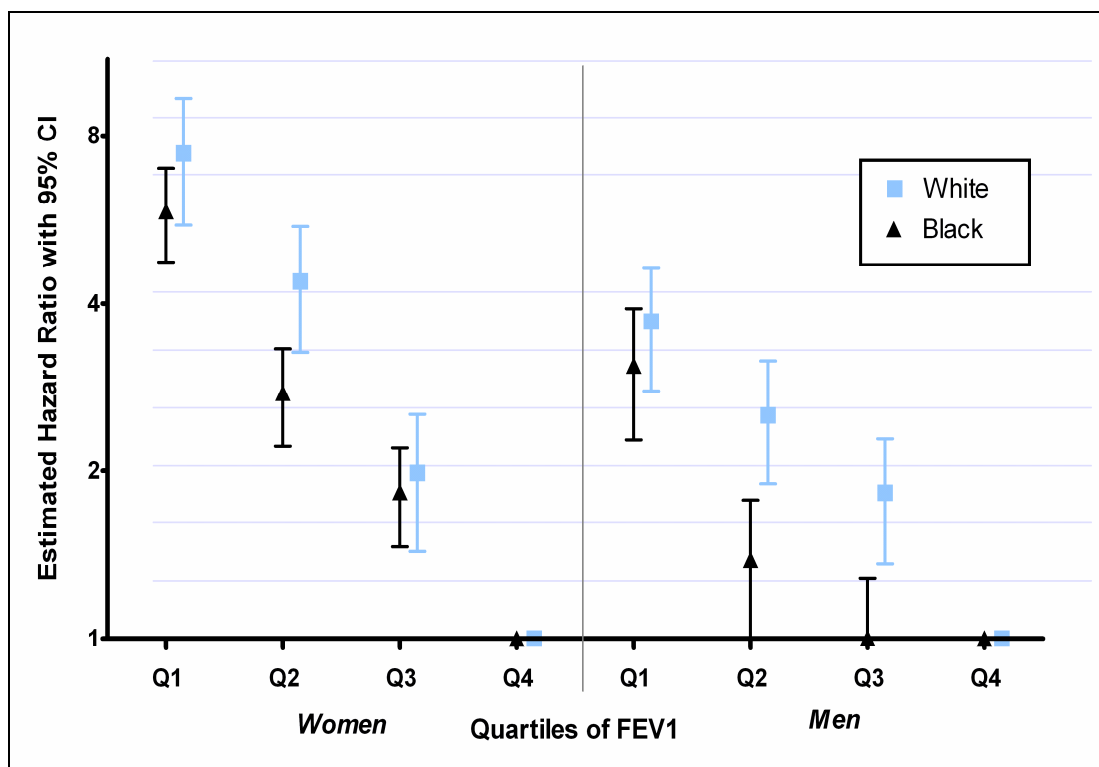Hazard ratios and 95% confidence of incident HF contrasting the lowest quartile to the highest quartile of FEV1. FEV1 quartiles were race and gender specific, and the models contained quartiles as indicator variables to estimate the effect size without assuming log-linearity in FEV1 quartiles. The exclusions were made before making the quartiles of FEV1, except in the case where manipulation to index hospitalization events was done.

†Model 1: This model adjusts for age, height, height*height and smoking status by using two binary variables: current smoking, and former smoking, and cigarette-years of smoking.

‡Model 2: In addition to model 1 covariates, it adjusts for prevalent coronary heart disease, diabetes, hypertension, LDL cholesterol and HDL cholesterol.

Acute exacerbation of COPD was defined by the presence of ICD -9 code = 491.21 at any position in the discharge diagnosis or a mention in the medical record. Similarly, respiratory failure or insufficiency was defined by the presence of ICD- 9 code = 517.3, 518.5, 518.81, 518.82, 518.83, 518.84, 799.1, V461, V4611, V4612, V4613, V4614, or V462 at any position in the discharge diagnosis or a mention in the medical record.

B. Manuscript 2: Optimal prediction of heart failure in community settings: The Atherosclerosis Risk in Communities (ARIC) Study

Introduction

Each year about 500,000 individuals are diagnosed with Heart Failure (HF) for the first time in the U.S. (Rosamond, Flegal et al. 2008). Despite improvements in medical management and advances in therapy, the incidence and prevalence of HF have increased (Roger, Weston et al. 2004). While there has been progress in the therapy of HF leading to better survival during the last decades, many agree that greater efforts need to be directed towards early detection of ventricular dysfunction and prevention of symptomatic heart failure (Fonseca 2006). Early and accurate HF diagnosis can be viewed as the cornerstone of improved patient outcome (Fonseca 2006).

While most patients with HF present for the first time to general practitioners (GPs) and are mostly managed by them (Fowler 1997), the importance of early diagnosis and treatment of LV systolic dysfunction is not fully appreciated among general practitioners (Mair and Bundred 1996). A lack of confidence among primary care physicians in establishing an HF diagnosis has been reported as one of the main barriers to providing standard care to patients with HF in the community (Fuat, Hungin et al. 2003). To facilitate early diagnosis appropriate risk stratification tools may aid in timely referrals and appropriate diagnostic tests. Risk prediction from information easily available to primary care physicians is one such tool(Kannel, D'Agostino et al. 2004).

The HF risk score function derived in the Framingham Heart Study (Kannel, D'Agostino et al. 1999), and a recently published HF risk score from the Health, Aging, and

Body Composition(Butler, Kalogeropoulos et al. 2008) study are two extant functions.

External validation in an independent test data set is considered a requisite before the use

of such models can be recommended (Ripley 1996). This study examined the external

validity of the above risk scores in a large, bi-racial cohort of middle aged participants

sampled from four US communities. We also optimized a HF risk function in the ARIC

cohort that considers additional characteristics commonly available in primary care settings

and examined its performance relative to the Framingham and Health ACC functions in the

prediction of 10-year risk of HF. Lastly, the incremental value to HF risk prediction of

biomarkers recently found to be predictive of HF was examined since their use in clinical

settings is increasing. Thus, our aims were to examine the external validity of two extant HF

risk functions and to compare their performance to one derived in a community based

sample of middle-aged adults, based on elements easily available to primary care providers.

Methods

Study population

The ARIC Study enrolled 15,792 men and women ages 45-64 years sampled from

four U.S. communities: Forsyth County, NC; Jackson, MS; seven northwestern suburbs of

Minneapolis, MN; and Washington County, MD. Enrollment at the Jackson, MS site was

restricted to black residents, while black residents were over-sampled in Forsyth County.

Baseline examinations of the cohort were conducted from 1987 to 1989 to collect

standardized information on socioeconomic indicators, medical history, family history,

cardiovascular risk factors, serum chemistries, electrocardiograms (ECGs), medication use,

and lung volumes. Three re-examinations followed the baseline visit, as well as annual

telephone interviews and active surveillance of hospitalizations and death. The last

complete cohort visit was done in 1996-98. Several biomarkers were assayed from stored specimens from this last visit. A complete description of the ARIC communities and of the study design has been published [18].

Analysis involved use of covariates at two different index visits i.e., the baseline examination (1987-89) and the third re-examination or visit 4 (1996-98). For analyses using baseline data those with prevalent HF (n=775) or missing (n=325) data on HF at baseline (Loehr, Rosamond et al. 2008); missing information on any of the predictors shown in table 11 (n=1502); or race other than black or white (n= 48) were excluded,. thus leaving a cohort of 13,555 observations for analysis. From the 11,751 cohort members examined at the ARIC field centers during visit 4, those with prevalent HF at baseline visit (n= 622) and those with incident HF between baseline visit and visit 4 (n = 230) were excluded ; those not self-identified as black or white (n=30), and those missing any important covariate (n = 237) were excluded from the analyses using visit 4 as the index visit. This resulted in 9,144 study participants for these analyses.

Baseline data

Participants were requested to refrain from smoking and from consuming caffeinated beverages, and to fast for 12 hours before the field center visit. During the baseline visit participants were interviewed, an electrocardiogram was recorded, blood sample obtained and a physical exam was performed.

Predictors of heart failure Prevalent coronary heart disease (CHD) was ascertained using history elements as well as adjudicated baseline ECG. Following 5 minutes of rest and while

seated, blood pressure was measured three times using a random-zero sphygmomanometer and an average of the last 2 readings was taken. Hypertension was defined as diastolic pressure≥ 90 mm Hg or systolic pressure≥140 mm Hg on the average of the last two of three seated, measurements, or by a self-reported use of medications for hypertension. Serum glucose was measured using hexokinase method. Diabetes was defined by the presence of any serum glucose level >= 200 mg/dl, an 8-hour fasting glucose level >=126 mg/dl, a self-reported history of diabetes, or the current use of medications for diabetes. Cigarette smoking status was defined as self reported current smoking or a history of ever smoking four hundred cigarettes or more. The self reported average number of cigarettes/day and numbers of years of smoking were multiplied to derive cigarette-years of smoking and this number was divided by 20 to get pack-years of smoking. COPD was defined as a self report of physician diagnosis of either emphysema or chronic bronchitis (or a chronic lung disease when using visit 4 as baseline). Body mass index was defined as the ratio of measured weight (in kilograms) and measured height^2 (in meter^2). Participants identified themselves as belonging to American/Alaskan Indian, Asian, black, or white race.

An auscultatory finding of either a diastolic murmur or a systolic murmur of grade 4 or above by a trained physician assistant was considered as positive for presence of a valvular heart disease (VHD). A supine 12-lead ECG at rest was obtained using the MAC PC10 personal cardiogram (Marquette Electronics, Milwaukee, Wisconsin). Electrocardiographic data processing, monitoring, and quality control have been described elsewhere(Vitelli, Crow et al. 1998). The presence of left ventricular hypertrophy was defined as a Cornell voltage >28 mm in men or >22 mm in women when using a 12 lead resting ECG. A QRS duration of >120 ms on a 12 lead resting ECG was used to define prolonged QRS interval.

Using stored samples from visit 4 (1996-98), Cystatin C and high-sensitive C reactive protein (hs-CRP) were estimated in 2008. The Cystatin C assay employed particle-enhanced immunonephelometry (N Latex Cystatin C, Dade Behring, Inc., Deerfield, IL) with a BNII nephelometer (Dade Behring, Inc., Deerfield, IL) was used (Erlandsen, Randers et al. 1999). Measurement reliability for blinded quality control replicates of cystatin C was 0.94 after removing 10 replicate outliers pairs(Folsom, Lutsey et al.). CRP was measured using the immunoturbidimetric assay using the Siemens (Dade Behring) BNII analyzer (Dade Behring, Deerfield, Il, USA), and reliability coefficient for blind replicates was 0.99(Folsom, Lutsey et al. 2009).

All except two variables i.e., valvular heart disease and serum albumin, were available from the visit 4 examination. When using visit 4 as the index visit the baseline values of valvular heart disease and serum albumin were carried forward.

Heart Failure

Incident HF was defined as the first HF hospitalization or presence of HF code on death certificate since baseline visit. These events were identified from hospital discharge records and death certificates that showed a HF code in any position. International Classification of Diseases Code, Ninth Revision (ICD-9) code '428.x', and deaths with ICD-9/10 codes of either 428.x or I50 were considered as HF. Follow up for the current analysis ended on December 31, 2005.

Statistical Methods

Means (standard deviations) and proportions of characteristics at baseline were estimated by incident HF status. Performance measures such as Area Under the ROC Curve (AUC) and net reclassification improvement (NRI) were estimated for discrimination, and Gronnesby-Borgan (GB) statistics(Gronnesby and Borgan 1996) for model fit. By considering censoring in the context of long term risk prediction the AUC can be defined as the probability that a person with disease onset by time T_0 has a higher risk score than a person with no event by time T_0, $P(Z_i > Z_j \mid D_i(t) = 1 \ \& \ D_j(t) = 0)$ where D(t) is an indicator variable for event or no event by time t, and Z denotes risk score. In addition to AUC, the NRI for cut-offs (<5%, 5 to <10%, 10 to <20%, and 20% or more) was calculated (Pencina, D' Agostino RB et al. 2008; Pepe, Feng et al. 2008) since NRI is more meaningful for clinical decision making than the AUC (Pencina, D' Agostino RB et al. 2008). The NRI statistics cross tabulate the number of individuals classified into various risk levels (such as low, medium, and high) by two models. The movement of individuals between categories could be upward, downward, or no reclassification. Based on an individual's actual outcome, the full model may reclassify him/her appropriately (upward movement given an event and downward in the absence of an event), or inappropriately. The GB statistics were used to measure the goodness of fit of the risk score by deciles of the function. By computing the martingale residuals for each decile the GB statistic tests the hypothesis that the expected value of the sum of these residuals is equal to zero (May and Hosmer 1998).

Cox proportional hazard models were used to estimate age independent hazard ratios for presence vs. absence (categorical variables), and per SD increment (for

continuous variables). AUC and GB statistics were estimated for functions with age and each independent variable.

To test the external validity of the extant risk functions in the ARIC study first we estimated the risk score for each participant using published regression coefficients from the extant functions multiplying them by the respective variables. A Cox regression model was the fit with the risk function as the sole independent variable and performance statistics were estimated. We did this for both 5 and 10 years of follow up. The AUC estimates were stable after 5 years.

To estimate the ARIC risk function multivariable Cox regression with backward elimination (using a stay p value of 0.1) was fit to the full ARIC cohort. All variables in Table 11 except for race and gender were retained. The ARIC HF risk score was compared with both Framingham risk score and Health ABC risk score. For the estimation of performance statistics for the Framingham and the Health ABC risk scores we used both published regression coefficients(Kannel, D'Agostino et al. 1999; Butler, Kalogeropoulos et al. 2008), and regression coefficients derived within ARIC cohort using the variables in the respective risk scores.

To obtain stable estimates for AUC corrected for optimism (due to fitting the risk score in the same sample from which it was derived), 1000 bootstrap samples were processed since bootstrapping provides stable estimates with lower bias compared to split-sample and cross-validation (Steyerberg, Harrell et al. 2001), permits the use of the entire dataset and allows for the estimation of the error rates/the reduction of bias of effect

estimates. The average optimism i.e., (measure $_{bootstrap\ samples}$ − measure $_{original\ dataset}$) was subtracted from the original performance measure.

The incremental value of biomarkers was evaluated using ARIC visit 4 as baseline and fitting a basic model without biomarkers and a full model that included biomarkers. AUC, NRI, and GB statistics were estimated to compare the risk functions.

Results

Over the course of 15.5 years if follow-up an incident HF event occurred in 1487 of the 13,555 participants (11%). When using the 4th cohort examination as baseline, 647/9144 (6.6%) of the cohort members developed HF through 2005, for an average follow up of 7.9 years.

Table 11 describes the characteristics at baseline by incident HF status, The age adjusted hazard ratio (HR) and corresponding 95% confidence interval (95% CI) for the presence of the characteristic or per unit increase in the standard deviation, the AUC and the GB statistics are also shown in Table 11. Briefly, diabetes/blood glucose, hypertension/systolic blood pressure, BMI, and pack years of smoking contributed most to the AUC as increments to the AUC derived from a model that includes only age. When using backward elimination in the full cohort with p<=0.1 to retain a variable all variables include in Table 11 were retained, except for gender and race. Thus, the ARIC HF risk score included the following variables: age, race, gender, prevalent CHD, valvular heart disease, left ventricular hypertrophy, hypertension, diabetes, QRS duration >120 ms,

smoking status, pack-years of smoking, COPD, systolic blood pressure, heart rate, HDL

and LDL cholesterol, body mass index, fasting glucose, serum creatinine and albumin..

Table 12a-b presents these variables and their corresponding beta coefficients and hazard

ratios overall, and by race and gender. Some variability in the magnitude and direction of

associations may be seen by race and gender but there is limited statistical power to

characterize these associations in subsets of the cohort. **Table 13** presents the AUC and

model fit statistics for ARIC, Framingham and the Health ABC risk functions. For the latter,

the AUC were estimated using the published beta estimates from the respective cohorts

and also estimated in the ARIC cohort using the variables included in the Framingham and

the Health ABC HF risk scores, respectively. The AUC from the ARIC HF risk function was

higher at 0.8101, 95% CI = 0.8065, 0.8125 (optimism corrected = 0.808) than the AUC

estimated in the ARIC cohort using variables from the Framingham HF risk score (0.7618),

and with the variables in the Health ABC risk score (0.7835). The AUC using published

coefficients from the Framingham and the Health ABC HF risk scores were 0.6139, and

0.7848, respectively. Addition of the biomarkers cystatin C and hs-CRP to the ARIC HF risk

score improved the AUC by 0.004, NRI = 5.2% (Table 14 and 15a).

Reclassification using the ARIC HF risk score improved overall classification for

23.5% individuals compared to Framingham HF risk score, and 12.8% compared to Health

AB HF risk score (**Tables 15b – 15c**). The overall goodness of fit by decile of risk score

was good for the three risk functions, although the sensitivity of the GB test to the large

number of events lead to a p<0.001 for all test risk scores.

Figure 7 shows the observed vs. predicted event rates/frequencies by deciles of risk score

using published beta estimates from the Framingham and Health ABC studies. The

discrimination as well as fit to the ARIC cohort using Framingham risk score appear to be poor, whereas the Health ABC estimates fit well to the ARIC cohort. **Figure 8** displays the predicted and observed events in the ARIC cohort from the ARIC risk function, by decile of risk prediction score. In **Figure 9** the ten-year predicted risk of HF by deciles of three risk functions are shown, as derived in the ARIC cohort using variables from Framingham and the Health ABC HF risk scores.

Discussion

We derived a function to estimate the 10-year risk of incident HF in a population sample of men and women aged 45-64 years, using variables easily available to the primary care physician. Compared to the extant HF risk scores this ARIC HF risk function performed better in terms of discrimination, using both traditional (Area Under the Curve) and novel (Net Reclassification Improvement) statistics when using the variables or published coefficients from the existing risk scores. The NRI was 23.5% using Framingham variables fit in the ARIC cohort; the corresponding NRI when compared to the Health ABC variables was 12.8%. Overall, the goodness of fit across decile of risk was satisfactory.

The Framingham HF risk score did not perform well in this sample of middle aged blacks and whites drawn from four US communities, even when applied to whites with either hypertension or valvular heart disease, or left ventricular hypertrophy. The discrimination achieved using the Health ABC risk score, based on a cohort of healthy older adults, was good. The addition of few variables used in the ARIC HF risk score did improve the AUC and net reclassification obtained with the Health ABC HF function.

Heart Failure is the culmination of diverse and complex pathological processes resulting in insufficiency by the heart to circulate blood at normal pressures to meet physiologic needs (Braunwald, Zipes et al. 2001). In this respect it is of interest to see a discrimination ability for HF, e.g., the AUC, considerably higher than what is generally seen for CHD risk prediction, especially among women(D'Agostino, Grundy et al. 2001). Heart rate, ECG-defined left ventricular hypertrophy, and the QRS interval are readily available to a primary care physician from a 12 lead ECG. Similarly, BMI, smoking status, history of COPD, and laboratory parameters such as serum albumin, cholesterol, typically are available. The inclusion of the latter variables in the prediction of HF improves AUC by about 5% and leads to NRI of 23.5% relative to the Framingham HF risk score.

Though prognostic risk scores are commonly used in clinical practice for many diseases such as breast cancer, coronary heart disease, mortality post organ transplant among others, the use of such tools in the prediction of HF may not be widespread. Barriers to their use need examination. One can posit that risk scores are accepted and optimally useful in clinical practice if they are perceived to be consistent with clinical guidelines that frame the evaluation and management of the conditions they focus on. Convenient access to the predictor variables in the risk score, ease of use, parsimony in the number of predictor variables and the ability to modify the factors that adversely influence a patient's risk also seem influential for acceptability in clinical practice. Optimizing a risk score for use in clinical practice was not in the scope of the current work.. However, such work is an important as a step to draw on the desirable properties of the model developed here. A risk score with these characteristics that can penetrate clinical practice can serve to identify patients at intermediate predicted risk levels who may benefit from timely use of diagnostic

testing such as echocardiogram, referral to cardiologist, and regularly scheduled visit. Similarly, those at high levels of predicted risk would be identified as candidates for aggressive management of risk factors to delay development of HF and improve outcomes.

Among the strengths of this study is the derivation of a risk score in a large community-based cohort of middle aged white and black men and women, with long term follow-up and high retention rates. There are also limitations worth noting. Although similar to that of the Health ABC study and other cardiovascular disease cohorts, the classification of HF as the outcome was not validated. A recent validation study based on a large sample of hospitalizations discharged with ICD codes with high suspicion of HF indicates that the predictive value positive (PPV) of an ICD code '428.x' for HF classified by a physician review panel was 77%, and the sensitivity was 95% (Rosamond, Chang et al. 2009). The corresponding PPV and sensitivity of Framingham Heart Failure criteria were 0.78, and 0.83, respectively(Rosamond, Chang et al. 2009). Thus, the HF outcome based on hospital discharge ICD codes used in our analyses may be considered at least as good as the Framingham HF diagnostic criteria. However, it should be noted that our study would miss HF cases managed successfully in outpatient settings if they were not hospitalized throughout the 15.5 year follow up period.

The performance in, and generalizability to non-white, non-black groups of the ARIC HF risk score and equivalent risk functions need to be examined. There is a remarkable lack of information in this regard. Replication of our study findings in other population based cohorts is required, and may result in calibration according to differences in risk of HF. Future studies are also encouraged to consider the addition of biomarkers predictive of HF,

to test whether improvements in risk prediction can be achieved while considering the costs and benefits of their inclusion.

We conclude that the ARIC HF risk score performs well in predicting 10-year risk of hospitalized HF in community settings, with results based on a large cohort of middle aged black and white men and women. The performance of this risk score appears to be better than that of extant HF risk scores. These findings need replication, and possibly calibration, in other cohorts. Early identification of susceptibility to HF and its efficient monitoring in community settings may contribute to proactive risk management and to the reduction in the growing burden of decompensated HF.

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Table 11. Characteristics at baseline by heart failure during follow up, age adjusted hazard ratios, AUC, and GB statistics

Characteristics	HF during follow up*		SD	Hazard ratio[¶]			AUC[‖]	Gronnesby-Borgan test[§]	
	Yes (n=1487)	No (n=12068)		HR	95%CI			Chi-square	P value
Age[#] (years)	56.6	53.8	5.8	1.69	1.60	1.78	**0.638**	6.73	0.665
Male	0.54	0.44		1.43	1.29	1.58	0.653	2.12	0.990
Black	0.34	0.25		1.78	1.60	1.98	0.660	18.33	0.032
Prevalent CHD	0.13	0.03		4.23	3.63	4.93	0.669	23.25	0.006
Valvular heart disease	0.04	0.01		2.72	2.12	3.50	0.645	15.56	0.077
Left ventricular hypertrophy	0.06	0.01		3.89	3.15	4.80	0.652	23.29	0.006
Hypertension	0.54	0.3		2.34	2.11	2.60	0.684	19.84	0.019
Diabetes	0.29	0.08		3.86	3.45	4.32	0.695	50.30	0.000
QRS duration >120 ms	0.07	0.03		2.32	1.91	2.82	0.648	7.35	0.601
Current smoking	0.37	0.24		2.14	1.92	2.38	0.672	6.88	0.649
Former smoking	0.32	0.32		0.95	0.86	1.06	0.643	4.84	0.848
COPD	0.12	0.08		1.63	1.39	1.90	0.646	13.19	0.154
Systolic blood pressure (mmHg)	130.0	119.8	18.7	1.48	1.42	1.55	0.689	25.52	0.002
Heart rate (beats/minute)	68.9	66.2	10.2	1.31	1.25	1.37	0.668	11.48	0.244
HDL cholesterol (mg/dl)	47.2	52.7	17.0	0.68	0.64	0.72	0.678	13.01	0.162
LDL cholesterol (mg/dl)	143.3	136.9	39.1	1.47	1.40	1.53	0.652	12.83	0.170
Body mass index (kg/(m*m))	29.6	27.3	5.2	1.47	1.40	1.53	0.687	12.01	0.213
Fasting glucose (mg/dL)	130.2	104.6	37.4	1.38	1.34	1.41	0.685	93.84	0.000
Log (serum creatinine in mg/dl)	0.1	0.1	0.2	1.26	1.21	1.32	0.665	16.23	0.062
Serum albumin (mg/dL)	3.8	3.9	0.3	0.72	0.69	0.76	0.674	7.59	0.576
Pack-years of smoking	24.0	14.6	21.3	1.37	1.32	1.43	0.680	14.93	0.093

SD = Standard Deviation, AUC = Area Under Curve of a receptor operating function, CHD = Coronary Heart Disease, COPD = Chronic Obstructive Pulmonary disease (self report of a physician diagnosis)

[*] Expressed as Mean and Standard deviation (SD) or Percentages

[¶] Each row represents a model. For variables other than age, models includes age as a simultaneous independent variable; hazard ratio contrasts presence of a categorical characteristics versus its absence; and per SD unit increase in the continuous variable, independent of age.

[‖] AUC is calculated over 10 years of follow up

[§] GB test has 9 degree of freedom corresponding to nine indicator variables to represent deciles.

[#] Model has only age as an independent variable

Table 12a. Regression coefficients (log of hazard ratio of heart failure) from multivariable models fit with the variables in the basic ARIC heart failure risk score, for all participants and by race and gender ; the ARIC cohort

Variables	All*	White		Black	
		Women	Men	Women	Men
Prevalent CHD	1.170	1.355	1.286	0.563	0.941
Valvular heart disease	0.660	0.451	0.616	1.051	0.583
Left ventricular hypertrophy	0.702	1.026	0.831	0.942	0.344
Hypertension	0.257	0.434	0.166	-0.075	0.534
Diabetes	0.522	0.553	0.507	0.631	0.622
QRS duration >120 ms	0.473	0.668	0.449	-0.268	0.687
Current smoking	0.791	1.051	0.661	0.759	0.380
Former smoking	0.149	-0.025	0.081	0.268	0.031
COPD	0.345	0.609	0.227	0.170	-0.124
Age (years)	0.068	0.081	0.075	0.059	0.045
Systolic blood pressure (mm Hg)	0.011	0.009	0.013	0.011	0.010
Heart rate (beats/minute)	0.018	0.018	0.021	0.015	0.021
HDL cholesterol (mg/dl)	-0.006	-0.003	-0.004	-0.003	-0.017
LDL cholesterol (mg/dl)	0.002	0.000	0.002	0.001	0.002
Body mass index (kg/(m*m))	0.045	0.058	0.065	0.029	0.022
Fasting glucose (mg/dL)	0.004	0.004	0.003	0.005	0.001
Log (serum creatinine in mg/dl)	1.004	0.630	0.434	1.240	0.447
Serum albumin (mg/dL)	-0.816	-0.409	-1.031	-0.765	-1.149
Pack-years of smoking	0.007	0.007	0.007	0.007	0.008

CHD = Coronary Heart Disease, COPD = Chronic obstructive Pulmonary Disease,
*In the full model with above variables and also race and gender fitted to the ARIC cohort, race and gender are dropped when using backward elimination and a p-stay = 0.1. Also, all variables had a p<0.001 except for former smoker (0.047), LDL (0.016), and HDL (0.001)
For white female the following variables were dropped at 0.1 level: Former smoking, HDL-C, LDL-C, and VHD
For black female the following variables were dropped at 0.1 level: Former smoking, HDL-C, Prolonged QRS interval, and Hypertension.
For white male the following variables were dropped at 0.1 level Former smoking, HDL-C, creatinine, and COPD
For black male the following variables were dropped at 0.1 level: Former smoking, LDL-C, glucose, and BMI

Table 12b. Heart failure hazard ratio estimates from multivariable models fit with the variables in the basic ARIC heart failure risk score, for all participants and by race and gender ; the ARIC cohort

Variables	All*	White		Black	
		Women	Men	Women	Men
Prevalent CHD	3.22	3.88	3.62	1.76	2.56
Valvular heart disease	1.93	1.57	1.85	2.86	1.79
Left ventricular hypertrophy	2.02	2.79	2.30	2.57	1.41
Hypertension	1.29	1.54	1.18	0.93	1.71
Diabetes	1.69	1.74	1.66	1.88	1.86
QRS duration >120 ms	1.61	1.95	1.57	0.77	1.99
Current smoking	2.21	2.86	1.94	2.14	1.46
Former smoking	1.16	0.98	1.09	1.31	1.03
COPD	1.41	1.84	1.26	1.19	0.88
Age	1.48	1.59	1.54	1.40	1.29
Systolic blood pressure	1.23	1.19	1.27	1.22	1.21
Heart rate	1.21	1.20	1.23	1.17	1.24
HDL cholesterol	0.90	0.96	0.93	0.94	0.76
LDL cholesterol	1.06	1.02	1.08	1.05	1.08
Body mass index	1.27	1.35	1.41	1.16	1.12
Fasting glucose	1.17	1.17	1.12	1.22	1.04
Log (serum creatinine)	1.21	1.12	1.08	1.26	1.09
Serum albumin	0.81	0.90	0.76	0.82	0.74
Pack-years of smoking	1.17	1.17	1.17	1.15	1.18

The hazard ratio for continuous variable are given per standard deviation (from the overall cohort)

Table 13. Discrimination and Goodness of Fit statistics for models optimized to predict the 10-year risk of heart failure

Sample		Area Under Curve					Gronnesby-Borgan chi-square (p value)				
		Framingham		Health-ABC		ARIC basic	Framingham		Health-ABC		ARIC-basic
		Published beta	Derived beta	Published beta	Derived beta		Published beta	Derived beta	Published beta	Derived beta	
All		0.614	0.762	0.785	0.783	0.812	<0.001	<0.001	<0.001	<0.001	<0.001
	Male	0.727	0.764	0.772	0.773	0.801	<0.001	<0.001	<0.001	<0.001	<0.001
	Female	0.700	0.766	0.790	0.790	0.820	<0.001	<0.001	<0.001	<0.001	<0.001

Table 14. Discrimination and goodness of fit statistics comparing the basic ARIC heart failure risk score model with a full model including biomarkers

	ARIC basic	ARIC biomarkers
AUC	0.790	0.794
GB test chi-square	28.61	27.15
GB p value	0.0008	0.001

AUC = Area Under Curve; GB = Gronnesby-Borgan statistics
Additional biomarkers include cystatin-C and high sensitive C reactive protein.

Table 15a. ARIC basic model — ARIC HF Risk score model with biomarkers

ARIC basic model	<5%			5 to <10%			10 to <20%			20% or more			Overall		
	n	row %	Risk	n	row %	Risk	n	row %	Risk	n	row %	Risk	n	%	Risk
<5%	5031	96.05	0.022	205	3.91	0.068	1	0.02	0	1	0.02	0	5238	53.5	0.024
5 to <10%	253	10.91	0.013	1911	82.41	0.063	148	6.38	0.181	7	0.3	0.143	2319	23.69	0.066
10 to <20%	0	0	.	176	12.95	0.131	1096	80.65	0.153	87	6.4	0.446	1359	13.88	0.163
20% or more	0	0	.	0	0	.	79	9.03	0.188	796	91	0.369	875	8.94	0.351
Overall	5284	53.97	0.022	2292	23.41	0.069	1324	13.52	0.157	891	9.1	0.369	9791	100	0.08

NRI   0.05248

ARIC = Atherosclerosis Risk In Communities Study, NRI = Net Reclassification Improvement ; basic refers to model without biomarkers but only variables routinely available to primary care physicians.
Additional biomarkers include cystatin C and C-reactive protein

Table 15b. Net improvement on reclassification of individual risk of heart failure using the variables in the basic ARIC risk score and those in the Framingham heart failure risk score

ARIC- basic HF Risk Score model

Framingham Risk Model	<5%			5 to <10%			10 to <20%			20% or more			Overall Sample		
	N	row %	Risk	n	row %	Risk	n	Row %	Risk	n	row %	Risk	n	%	Risk
<5%	8742	90.23	0.014	830	8.57	0.079	106	1.09	0.119	11	0.11	0.273	9689	71.48	0.021
5 to <10%	1046	45.05	0.031	815	35.1	0.075	378	16.28	0.178	83	3.57	0.348	2322	17.13	0.08
10 to <20%	62	5.81	0.05	371	34.77	0.092	427	40.02	0.171	207	19.4	0.344	1067	7.87	0.166
20% or more	2	0.42	0	23	4.82	0	127	26.62	0.173	325	68.1	0.382	477	3.52	0.303
Overall	9852	72.68	0.016	2039	15.04	0.079	1038	7.66	0.168	626	4.62	0.363	13555	100	0.051

NRI   0.235

Framingham = Framingham Heart Failure Risk Score model; ARIC = Atherosclerosis Risk In Communities Study, NRI = Net Reclassification Improvement ; basic refers to model without biomarkers but only variables routinely available to primary care physicians.

Table 15c. Net improvement on reclassification of individual risk of heart failure using the variables in the basic ARIC risk score and those in the Heath-ABC heart failure risk score

ARIC-basic HF Risk Score model

Health ABC Risk Model	<5%			5 to <10%			10 to <20%			20% or more			Overall Sample		
	n	row %	Risk	n	row %	Risk	n	row %	Risk	n	row %	Risk	n	%	Risk
<5%	9145	93.78	0.014	563	5.77	0.064	42	0.43	0.074	2	0.02	.	9752	71.94	0.017
5 to <10%	698	30.24	0.042	1215	52.64	0.083	368	15.94	0.171	27	1.17	0.224	2308	17.03	0.087
10 to <20%	9	0.92	0	259	26.35	0.091	523	53.2	0.157	192	19.5	0.325	983	7.25	0.171
20% or more	0	0	.	2	0.39	0.5	105	20.51	0.257	405	79.1	0.395	512	3.78	0.367
Overall	9852	72.68	0.016	2039	15.04	0.079	1038	7.66	0.168	626	4.62	0.363	13555	100	0.051

NRI   0.128

Health ABC = Health ABC Study Heart Failure Risk Score model; ARIC = Atherosclerosis Risk In Communities Study, NRI = Net Reclassification Improvement ; basic refers to model without biomarkers but only variables routinely available to primary care physicians.

Figure 7. Panel a. Four-year observed and expected HF events by decile of linear risk, estimated by applying published Framingham beta estimates to the ARIC cohort (year-year), Panel b. Fifteen-year observed and expected HF events by decile of linear risk, estimated by applying published Health-ABC beta estimates to the ARIC cohort , (1987-2005).
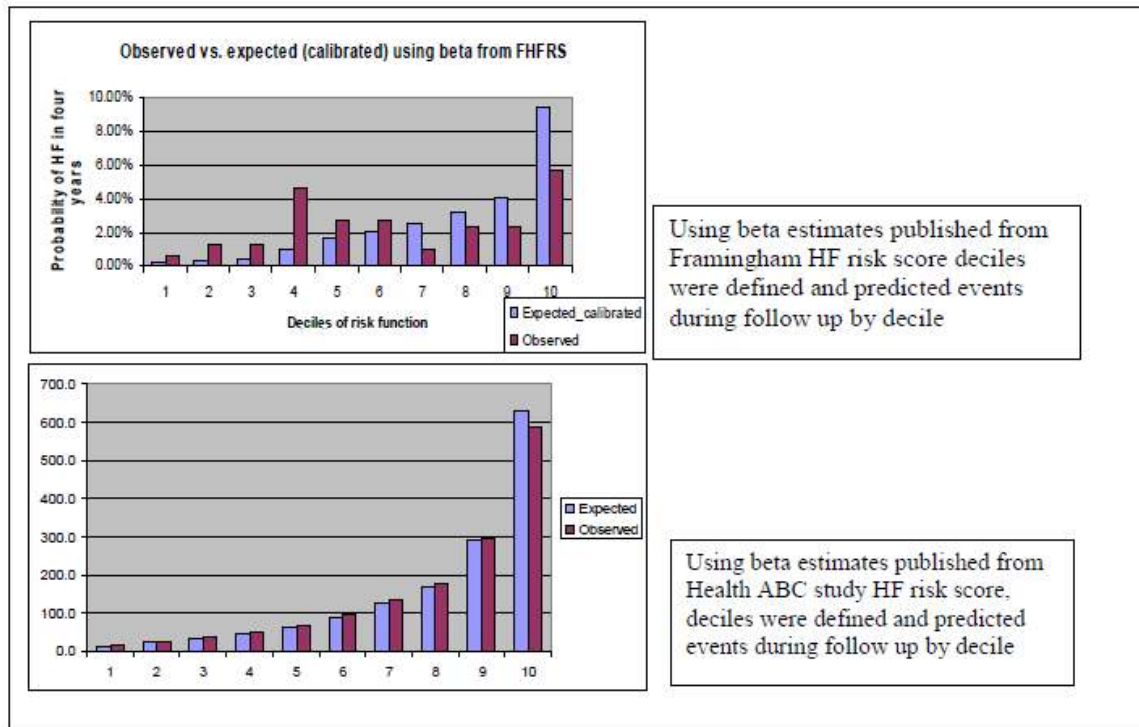
Figure 7. Panel a. Four-year observed and expected HF events by decile of linear risk, estimated by applying published Framingham beta estimates to the ARIC cohort (year-year), Panel b. Fifteen-year observed and expected HF events by decile of linear risk, estimated by applying published Health-ABC beta estimates to the ARIC cohort , (1987-2005).
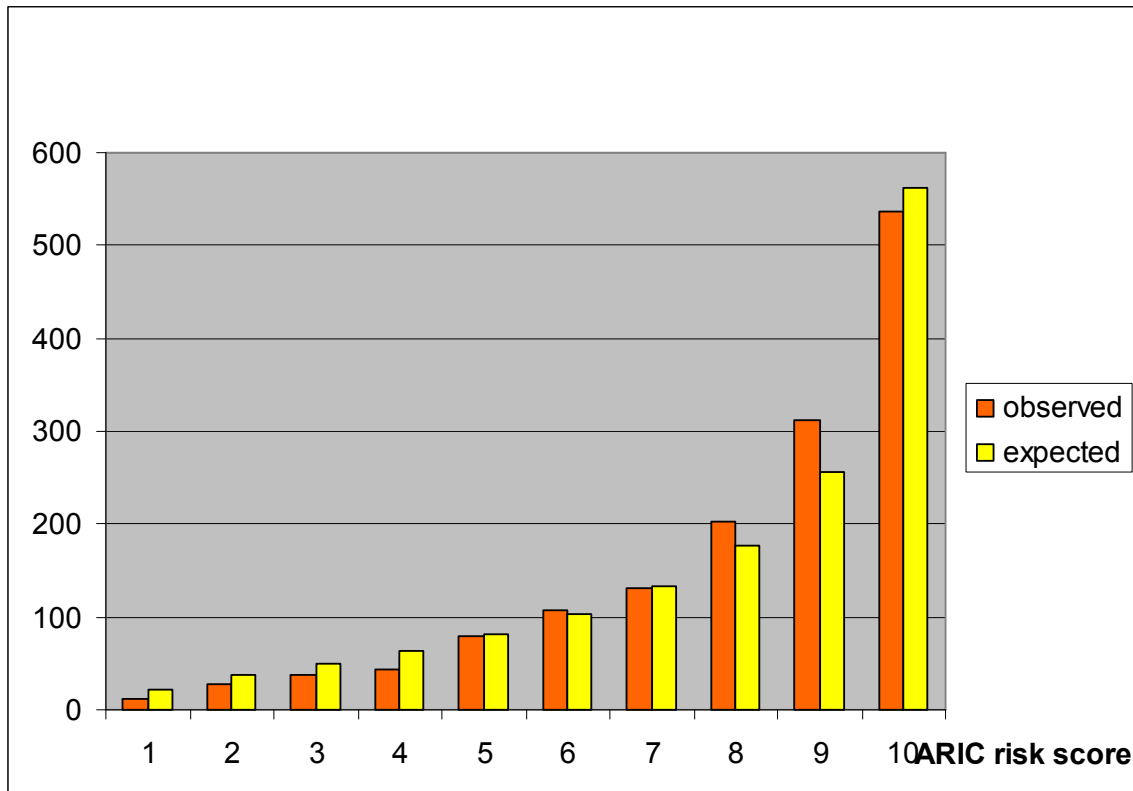

Figure 8. Number of observed versus predicted heart failure events during study follow up by decile of the ARIC heart failure risk score. Each decile includes approximately 1355 individuals at study baseline.
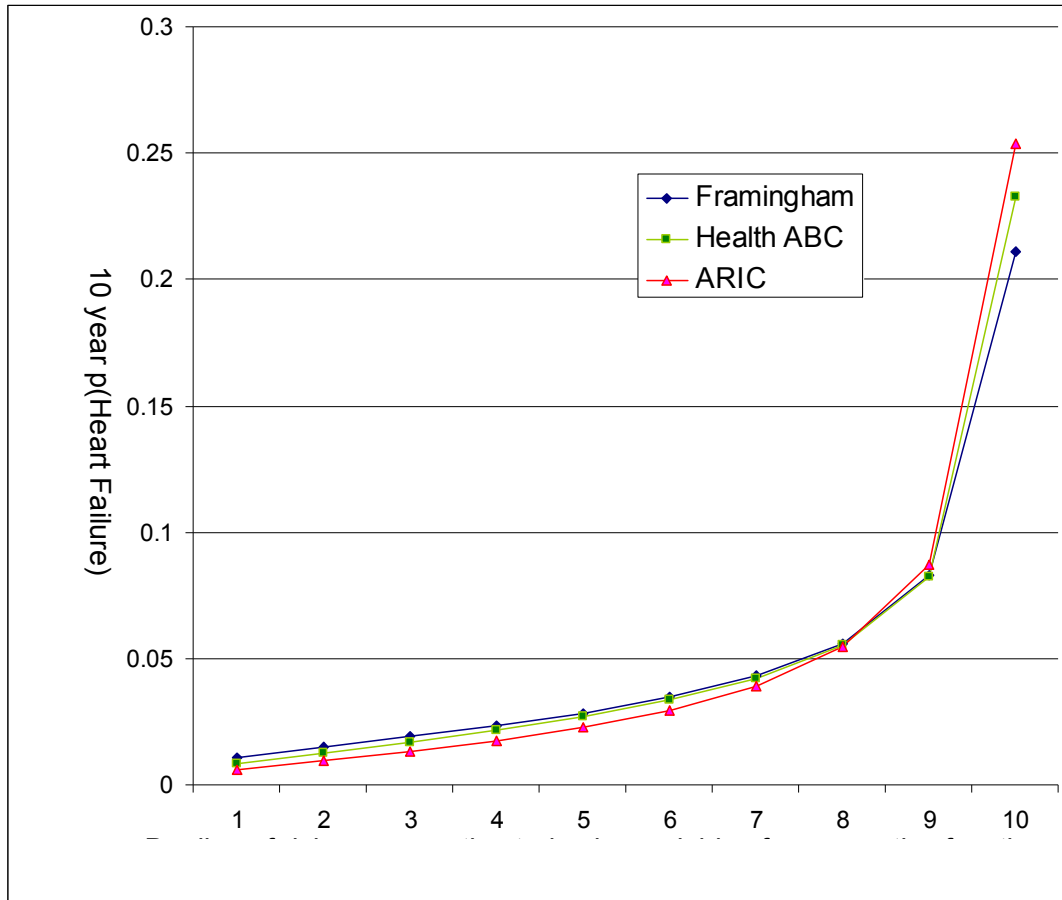
Figure 9. Ten year probability of heart failure by the decile of risk of the Framingham, Health ABC, and ARIC heart failure risk functions as fit on the full ARIC cohort.

Chapter V

V. CONCLUSIONS

A. Recapitulation

This project examined the association of obstructive airway disease (lung function) and incident heart failure in a large population based cohort. Also, it evaluated the external validity of two extant risk scores to predict heart failure, developed a novel risk score to predict ten years risk of heart failure in community settings, and tested the incremental value of two biomarkers to risk prediction.

B. Discussion of results

We observed a strong inverse association between baseline lung function with incident HF, and a monotonic, direct association between airflow obstruction and incident HF. These associations were seen across groups defined by race, gender, and smoking status. Notably, the relationship was seen in never-smokers and after adjustment for smoking status and cigarette-years of smoking, indicating that our results are not primarily confounded by smoking.

These results in a population-based cohort are consistent with clinical observations, but also with two prior reports from population based cohorts. The present study extends these results by the length and completeness of its follow-up, a replication in African Americans, and by examination of markers of chronic inflammation a potential mechanism.

Also, consistent association of interviewer-ascertained chronic bronchitis, self reported COPD and emphysema, and airway obstruction (FEV1/FVC<70%) with incident HF, but not with asthma was found. The weak but statistically significant association of asthma with incident HF among women could be explained by misdiagnosis of COPD for asthma in primary care, reportedly more common in women than in men. Our results are similar to those of a large retrospective case control study based on claims data. These associations were seen with moderate/severe COPD (defined with spirometry) and not with mild disease. Consistent association by race, gender, smoking group; replication of study findings in at least one other cohort; and several potential mechanisms explaining this association suggest that these results are robust.

While the Framingham HF risk prediction model did not perform well when applied to the ARIC cohort, the Health ABC risk function performed well. The ARIC HF risk score includes additional variable easily available to primary care physicians and had a better performance as quantified by an appropriate reclassification of individuals' risk compared to either Framingham or Health ABC risk score. Further, through it we extended the risk score estimations to ten years. Two biomarkers predictive of HF in the ARIC cohort added only slightly to improvements in risk prediction. The results from this research need to be replicated in independent cohorts and additional biomarkers should be tested for their ability to further improve risk prediction.

In conclusion, in this large population based closed cohort study with long term follow up, we observed that low FEV1, low FVC, self reported COPD, and airway obstruction are associated with incident HF. Improved survival following CHD and an

increase in other risk factors have increased the pool of patients with HF. Given the profound implications of HF at the population level in terms of loss of quality of life, mortality and societal costs, the prevention of COPD through programs on smoking cessation, ambient air quality and occupational exposures may contribute to reduce the burden of HF.

The ARIC HF risk score appears to be a better tool for risk stratification of middle-aged individuals in community settings than the extant risk scores. If replicated in independent samples, this score may help in early identification, referral, and management of patients at high risk of future heart failure. This has strong potential to improve the primary prevention of decompensated HF.

C. Degree to which doctoral goals have been met
The Academic Policies Manual published by the Department of Epidemiology recommends that doctoral research show accomplishments in four areas, as follows: a). High degree of originality, b). Depth, c). Scholarship, and d). Writing skills. The manuscripts based on this doctoral research were prepared with input from the doctoral committee members, and other co-authors with expertise both in the substantive areas and in methodology.

We submit that this work meets the expectations for doctoral research to a significant extent. a) Originality: To our knowledge this study is the first to examine the prospective association between airway obstructive disease measured in several, complementary ways and incident HF. Thus, the study adds to the limited literature on

spirometry indexes and incident HF and examines the potential role of inflammatory/coagulation markers in this association. Further, this is the first community based study to develop a risk score to predict ten year-risk of heart failure, and it uses recently proposed methods to test the performance of risk prediction models. This is also the first study to examine the incremental value of C reactive protein to HF risk prediction. b). Depth: this project uses longitudinal data analysis from two broad perspectives i.e., exposure-disease association and risk prediction. Both traditional and novel methods for risk prediction are used for this purpose and substantive knowledge about the exposure, the outcome and its classification, and on optimism in the estimation of risk function performance were used for additional analysis. c). Scholarship: this work applied rigorous research methods and has a potential to aid in prevention and management of heart failure. The first manuscript was nominated a finalist for a prestigious award at the 2009 AHA Epidemiology conference. d). Writing skills: Beyond the present work, I have been able to contribute to the writing of several manuscripts during my doctoral training, several of which have been published in peer review journals.

D. Strengths and Limitations

The strengths of the study on airflow obstruction and HF include their prospective and population-based nature, their internal consistency including among non-smokers, the sizeable magnitude of hazard ratio estimates even after multivariable adjustment, and the imperviousness of the results to various sensitivity analyses. The strength of risk prediction of HF study includes development of a risk score in a large sample of community based black and white men and women to predict long term risk, well characterized predictors at

baseline, replication of performance using another baseline 12 years apart, and testing incremental value of two biomarkers to risk prediction.

Among the limitations, the most important is the lack of validation and detailed characterization of the heart failure events. Further, the respiratory symptoms and diagnoses were self reported and not validated. Perhaps less worrisome, smoking status was self reported and not validated with biomarkers, thus some residual confounding due to smoking could not be ruled out, and neither post bronchodilator lung function or total lung volume were measured. Lastly, although adjustment for BMI did not influence the estimates, residual confounding due to sleep apnea could not be ruled out.

E. Future Directions

Replication of study results in independent cohorts for both studies is required. Studies that have the capacity for better characterized heart failure outcome would be desirable for purposes of replication and could provide important information about potential pathways linking COPD with HF. Further, it remains to be examined whether additional biomarkers such as N-terminal Brain Natriuretic Peptide or hs-troponin can improve risk prediction of HF, either alone or in combination.

APPENDICES

A. IRB Certification

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by Google

Sunil Agarwal <sunilagarwal1@gmail.com>

IRB Notice

IRB <irb_no_reply@mailserv.grad.unc.edu>   Wed, Sep 3, 2008 at 8:04 AM
To: sunilagarwal@unc.edu
Cc: gerardo_heiss@unc.edu

To: Sunil Agarwal
Epidemiology
CB: 7435

From: Public Health-Nursing IRB

Date: 9/02/2008

RE: Determination that Research or Research-Like Activity does not require IRB Approval
Study #: 08-1451

Study Title: Relationship between Pulmonary Disease, Lung Function and Incident Hospitalized Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study

This submission was reviewed by the above-referenced IRB. The IRB has determined that this submission does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 (d or f) and 21 CFR 56.102(c)(e)(I)] and does not require IRB approval.

Study Description:

The goals of this study are to assess the relationship between chronic lung disease, lung function and incident HF. This study hypothesizes that poor lung function at study baseline in individuals without HF is associated with increased risk of subsequent HG; this relationship is stronger in those with CAD, smokers, and those with diabetes; and will be attenuated after adjustment for inflammatory, pro-coagulability and metabolic derangement markers.

If your study protocol changes in such a way that this determination will no longer apply, you should contact the above IRB before making the changes.

CC:
Gerardo Heiss, Epidemiology

IRB Informational Message—please do not use email REPLY to this address

Gmail
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Sunil Agarwal <sunilagarwal1@gmail.com>

IRB Notice

IRB <irb_no_reply@mailserv.grad.unc.edu>   Wed, Sep 3, 2008 at 8:03 AM
To: sunilagarwal@unc.edu
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To: Sunil Agarwal
Epidemiology
CB: 7435

From: Public Health-Nursing IRB

Date: 9/02/2008

RE: Determination that Research or Research-Like Activity does not require IRB Approval
Study #: 08-1450

Study Title: Optimal Predictors of Incident Hospitalized Heart Failure: the ARIC Cohort Study

This submission was reviewed by the above-referenced IRB. The IRB has determined that this submission does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 (d or f) and 21 CFR 56.102(c)(e)(l)] and does not require IRB approval.

Study Description:

The goals of this proposal are to define the most parsimonious set of information readily available in the primary care setting that is optimally predictive of incident HF in African American and white middle-aged men and women, to compare their performance to that of the Framingham risk score for HF, and to examine whether a simple, updated HF risk score equation has merit in clinical and public health settings. The PI proposes to perform these analyses in extent data from the Atherosclerosis Risk in Communities (ARIC) cohort, i.e. 15,972 men and women aged 45-64 years at baseline, drawn as a sample from four U.S. communities and followed from 1987 through 2007 for hospitalization and mortality attributed to HF.

If your study protocol changes in such a way that this determination will no longer apply, you should contact the above IRB before making the changes.

CC:
Gerardo Heiss, Epidemiology

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B. Supplemental Results, Manuscript 1

Table 16. Quartile boundaries of FEV1 and FVC by race and gender

Race	Gender	n		Lower Quartile	Median	Upper Quartile
Whites	Female	5431	FEV(1) (liters) FVC (liters)	2.21 2.98	2.54 3.36	2.84 3.74
	Male	4862	FEV(1) (liters) FVC (liters)	2.98 4.17	3.47 4.70	3.91 5.24
Blacks	Female	2063	FEV(1) (liters) FVC (liters)	1.93 2.52	2.24 2.87	2.53 3.23
	Male	1304	FEV(1) (liters) FVC (liters)	2.62 3.53	3.02 3.98	3.41 4.43

Table 17. GOLD classification and risk of incident heart failure: The ARIC study					
GOLD staging	#	% cohort	Row % incident HF	Rate Ratio (95%CI) Model 1	Rate Ratio (95%CI) Model 2
No lung disease	9760	71.5	7.9	1	1
At risk of COPD	301	2.2	10.6	1.45(1.01, 2.06)	1.32(0.92, 1.88)
Restrictive	609	4.5	23.2	3.07 (2.56, 3.67)	1.82 (1.51, 2.19)
Mild COPD	1492	10.9	8.9	0.92 (0.76, 1.11)	0.98 (0.81, 1.20)
Moderate COPD	1281	9.4	18.2	2.03 (1.74, 2.35)	1.60 (1.37, 1.87)
Moderate/severe COPD	217	1.6	29.6	3.95 (3.06, 5.10)	3.40 (2.60, 4.44)

Model 1 adjusts for age.
Model 2 adjusts for age, prevalent CHD, traditional CHD risk factors, and BMI.
Rate ratios generated using Proc Genmod routine and assuming Poisson distribution in SAS.
In model 1, the estimates are much larger in female than males. For e.g. Restrictive is (3.59 vs. 2.70); severe COPD is (5.00 vs. 3.98). Similarly, the estimates were much larger for whites than blacks, for e.g. for restrictive (3.97 vs. 1.74); and for Severe COPD (4.35 vs. 3.41).

In model 2, the estimates were much larger for females than males, for e.g. for restrictive (1.95 vs. 1.74); and for Severe COPD (4.37 vs. 2.84). Similarly, the estimates were much larger for whites than blacks, for e.g. for restrictive (2.25 vs. 1.25); but not for Severe COPD (3.48 vs. 3.58).

Table 18. Obstructive, and Restrictive, lung disease and incident heart failure					
GOLD staging	#	% cohort	Row % incident HF	Rate Ratio (95%CI) Model 1	Rate Ratio (95%CI) Model 2
No lung disease OR At risk of COPD OR Mild COPD	11553	84.6	8.1	1	1
Moderate/severe COPD	1498	11.0	19.9	2.32(2.04, 2.65)	1.84 (1.60, 2.12)
Restrictive	609	4.5	23.2	3.10 (2.60, 3.70)	1.67 (1.39, 2.01)
Model 1 adjusts for age. Model 2 adjusts for age, prevalent CHD, traditional CHD risk factors, and BMI.					

C. Supplemental Results, Manuscript 2
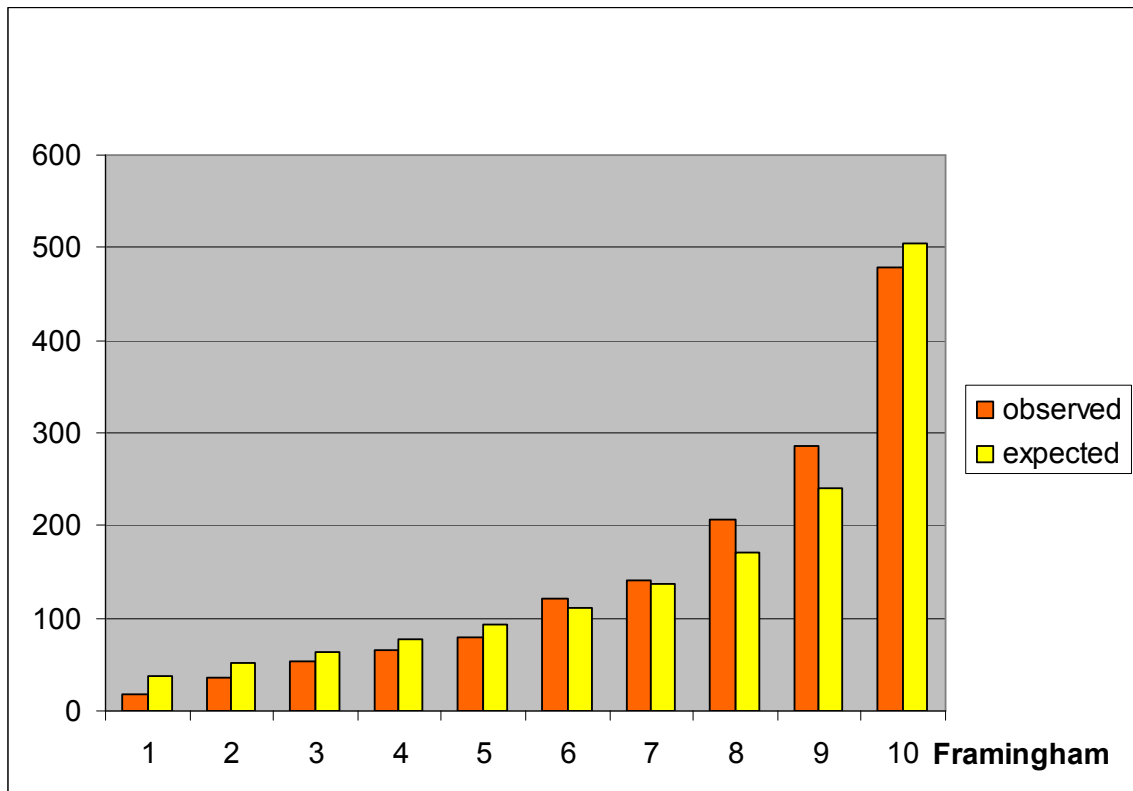

Figure 10. Number of observed versus predicted HF events during study follow up by decile of Framingham HF risk score. In each decile there were approximately 1355 individuals at baseline.
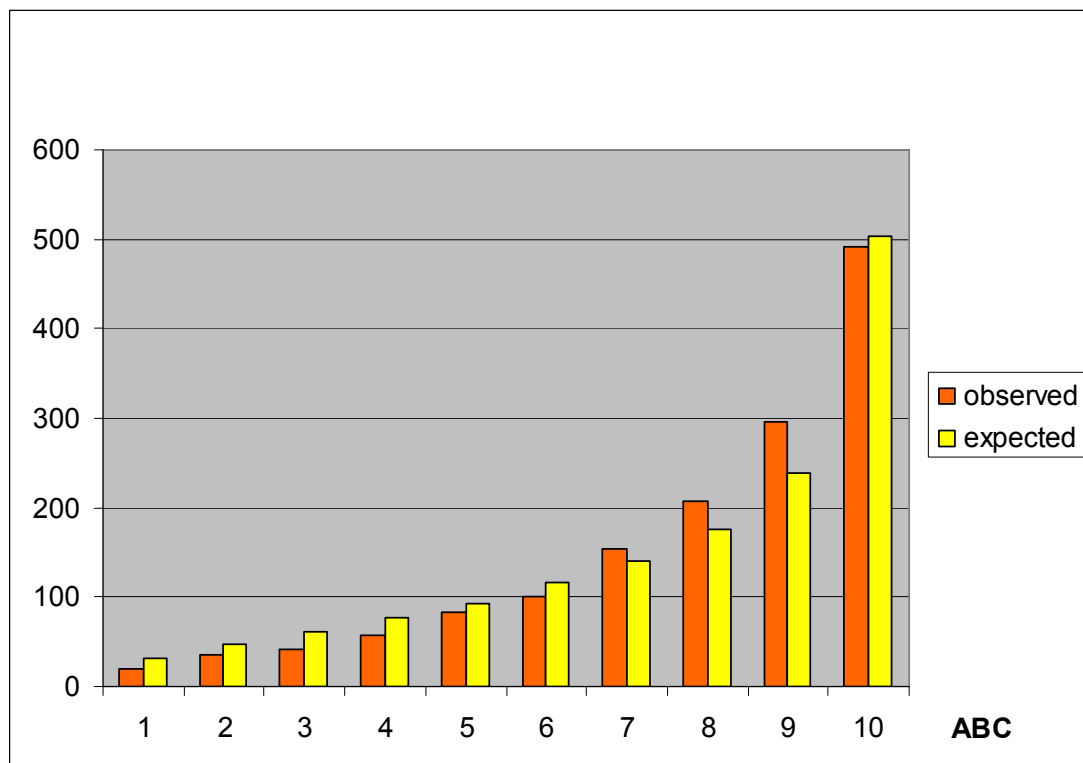
Figure 11. Number of observed versus predicted HF events during study follow up by decile of Health ABC HF risk score. In each decile there were approximately 1355 individuals at baseline.

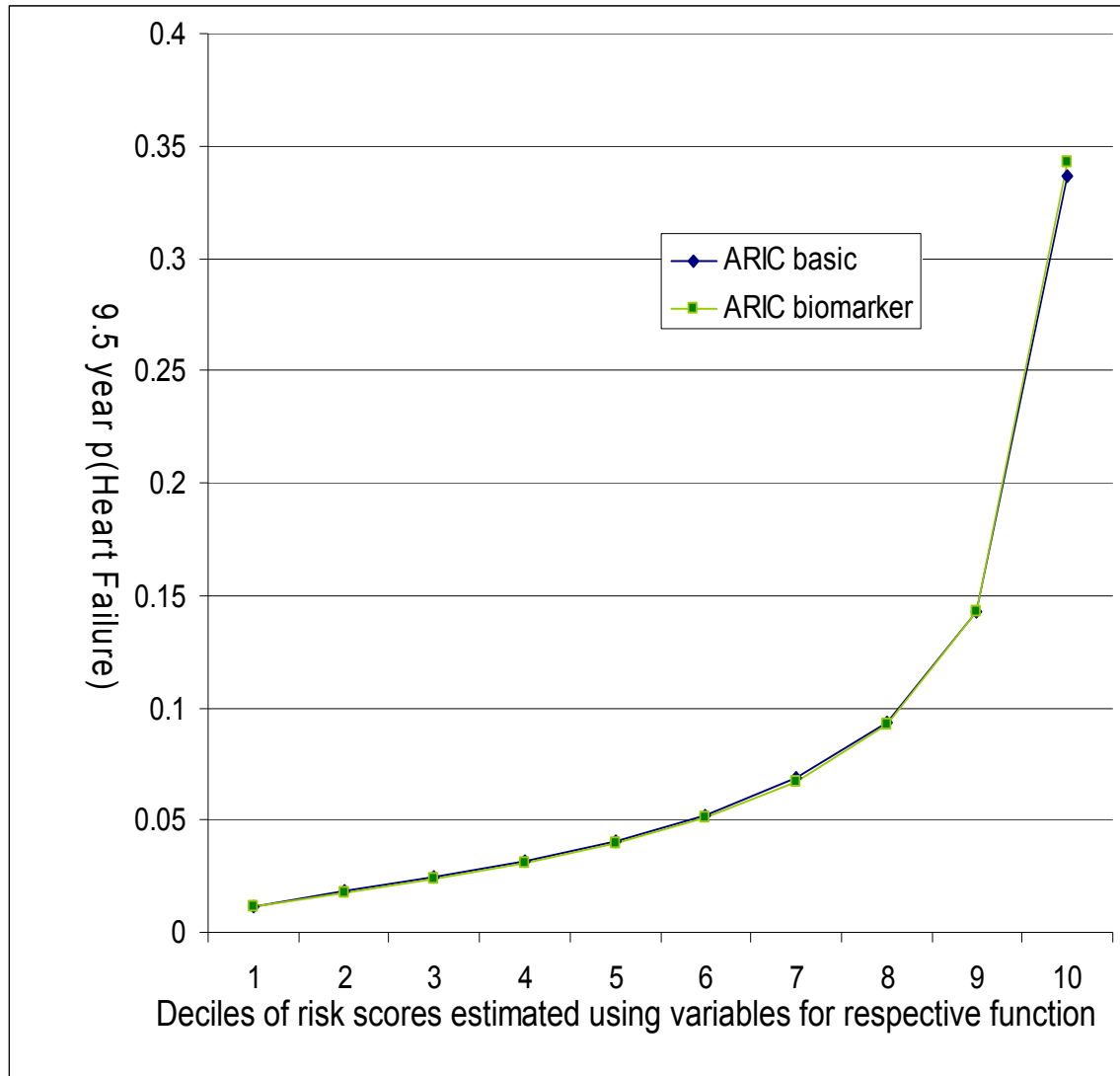Figure 12. Ten years probability of heart failure by the deciles of risk functions i.e. ARIC HF risk score, and ARIC HF risk score with addition of cystatin C and C reactive protein. Variables from respective risk score were fitted in multivariable models using the complete ARIC cohort.

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