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Troponin T, B type natriuretic peptide, C-reactive protein and cause-specific mortality

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Abstract

Purpose—To evaluate the associations of high sensitivity Troponin T (Hs-TnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high sensitivity C-reactive protein (Hs-CRP) with mortality from any cause, cardiovascular disease (CVD), coronary heart disease (CHD), stroke, cancer, and respiratory disease in the Atherosclerosis Risk in Communities (ARIC) cohort.

Methods—11193 participants aged 54-74 years, initially free of the conditions being studied, had biomarkers measured and were followed for a mean of 9.9 years.

Results—Hazard ratios (HR), adjusted for multiple risk factors, for mortality in participants in the highest Hs-TnT category compared to those with undetectable levels were: total 3.42 (95% Confidence Interval: 2.75-4.26), CVD 7.34 (4.64-11.6), CHD 6.06 (2.91-12.6), stroke 3.31 (1.26-8.66), cancer 1.60 (1.08-2.38) and respiratory 3.85 (1.39-10.7). Comparing the highest NT-proBNP quintile to those in the lowest quintile, the adjusted HRs for mortality were: total 3.05 (2.46-3.77), CVD 7.48 (4.67-12.0), CHD 4.07 (2.07-7.98) and stroke 10.4 (2.26-47.7). Comparing extreme Hs-CRP quintiles, the adjusted HRs for mortality were: total 1.61 (1.32-1.97), CVD 1.76 (1.19-2.62) and respiratory 3.36 (1.34-8.45). Having multiple markers elevated simultaneously greatly increased cause-specific mortality risks.

Conclusions—Greater levels of Hs-TnT, NT-proBNP and Hs-CRP are associated with increased risk of death, not just from cardiovascular disease but also from some non-cardiovascular causes.

Keywords

biomarkers; troponin T; B natriuretic peptide; C- reactive protein; mortality

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INTRODUCTION

Identification of novel biomarkers has helped increase understanding of the pathophysiology of diseases and improved the accuracy of diagnosis and disease prognosis. High sensitivity Troponin T (Hs-TnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (Hs-CRP) are distinct biomarkers that reflect cardiovascular disease (CVD) or inflammation. Troponin T elevation in plasma is usually considered to be due to cardiomyocyte necrosis. Recently, a Hs-TnT assay was developed to detect a 10- fold lower concentration than the conventional Troponin T assay. Hs-TnT has been shown to be positively associated with incident coronary heart disease (CHD), (1) heart failure, (1-2) cardiovascular mortality,(1-2) and all-cause mortality(1,3). NT-proBNP is synthesized in response to cardiac wall stress in conditions associated with volume overload. Plasma NT-proBNP is a strong predictor of heart failure, (4) and CVD mortality, (5) and long term mortality (6-7) in patients with acute coronary syndromes. Multimarker models have shown that NT-proBNP improves risk stratification of cardiovascular event in individuals with prevalent CVD.(8) Also a similar study with NT-proBNP, Troponin I, cystatin C and Hs-CRP combined improved risk stratification for CVD death in individuals with or without CVD.(9) Hs-CRP is a sensitive but non-specific marker of inflammation positively associated with cardiovascular disease incidence (10,11) and mortality (12-15) and all-cause mortality.(12-14) Though CRP is being used for risk stratification in the general population, there is still a lot of debate and limited information supporting its predictive role. (9,10,16) There are non-cardiac conditions where NT-proBNP and TnT elevation have been noted: for example, in patients with chronic hypercapnic respiratory failure in the absence of heart failure (17) and in intracranial hemorrhage or stroke,(18) respectively. Although there is some information on Hs-CRP and cause-specific mortality, there is little information for Hs-TnT and NT-proBNP and cause-specific mortality in the general population.

We therefore aimed to determine the independent association of Hs-TnT, NT-proBNP, and Hs-CRP with mortality from any cause, all CVD, CHD, stroke, cancer, and respiratory disease in participants in the Atherosclerosis Risk in Communities (ARIC) study. In addition, we evaluated the joint associations of elevated Hs-TnT, NT-proBNP, and Hs-CRP with cause-specific mortality.

METHODS

Study design and population

The ARIC study includes a prospective cohort of 15,792 participants, aged 45-64 years when recruited between 1987 and 1989, via probability sampling from four US communities (Jackson, MS; suburban Minneapolis, MN; Forsyth County, NC; and Washington County, MD). Participants were required to be residents of the communities with no definite plans to leave the area, mentally and physically able to participate, and free of language barriers to participation. ARIC examined the participants four times: 1987-89, 1990-92 (return rate=93%), 1993-95 (return rate=86%) and 1996-98 (return rate=80%, n=11668), with a fifth visit ongoing. Participants were also contacted yearly by telephone to inquire about their health status. This present analyses used visit 4 as their start point.

Measurement of biomarkers (independent variables)

Assays were recently performed on visit 4 (1996-98) plasma samples stored at -70°C. Troponin T levels were determined on a Cobas e411 analyzer using the Elecys Troponin T, a novel high sensitivity assay (Roche Diagnostics, Indianapolis, IN). The lower limit of detection is 0.003 ug/L. The reliability coefficient for blinded quality control replicate measurements (n=418 pairs) of Hs-TnT from single blood draws was 0.98. Plasma NT-

proBNP was measured on a Cobas e411 analyzer using the Elecys proBNP II immunoassay (Roche Diagnostics, Indianapolis, IN). The range of detection was 5- 35,000 pg/ml. The reliability coefficient for blind replicate measurements was 0.99 (N=418 pairs). CRP levels were assessed by the immunoturbidimetric CRP-Latex (II) high sensitivity assay from Denka Seiken (Tokyo, Japan) using a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis). The reliability coefficient for blind replicate measurements was 0.99 (N=55 pairs).

Measurement of other exposures

At visit 4, estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Epidemiology Collaboration Formula.(19) Plasma cholesterol (total and high density lipoprotein) and triglycerides were measured with standardized Monotest Cholesterol and Glycerolphosphate-oxidase Triglyceride procedures, respectively, using reagents from Boehringer Mannheim on a Roche Cobas Fara II analyzer.

Body mass index at visit 4 was calculated as weight in kilograms divided by the square of height in meters. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or use of antihypertensive medication in the past 2 weeks. Diabetes was defined as a fasting blood glucose of 126 mg/dl or higher, non-fasting blood glucose of 200 mg/dl or higher, use of antidiabetic medication in the past 2 weeks, or a physician diagnosis of diabetes. Standardized, questionnaires were used to ascertain medical history, cigarette smoking, and alcohol consumption at visit 4.

A few possible confounding variables were unavailable at visit 4 and were taken at earlier visits. Sports participation (20) and dietary intake were obtained at ARIC visit 3. Principal components-derived ‘Prudent’ and ‘Western’ dietary pattern scores were estimated using a 66-item food frequency questionnaire.(21) ‘Western’ diet was characterized by greater consumption of refined grains, processed meat, fried food, eggs, red meat, and soda, while the ‘Prudent’ diet was characterized by greater intake of vegetables, fruits, fish, seafood, poultry, whole grains, and low-fat dairy products. Forced expiratory volume in 1 second was determined at ARIC visit 2 with a Collins Survey II water-seal spirometer and was analyzed as a percentage of predicted FEV1.

Measurement of prevalent disease and mortality outcomes

Depending on the mortality outcome of interest, we excluded certain prevalent diseases at visit 4 from the at-risk cohort, and the definitions of the prevalent diseases were as follows. Prevalent CHD at visit 4 was defined as (a) a self-reported myocardial infarction (MI), ECG evidence of MI, or coronary revascularization reported at visit 1 or (b) incident MI (22), silent MI, or revascularization procedure before visit 4. Prevalent stroke at visit 4 was defined as (a) reporting a physician diagnosed stroke at visit 1 or (b) a definite or probable incident stroke (23) before visit 4. Prevalent heart failure (HF) at visit 4 was defined as (a) taking medications for HF or having HF by Gothenburg criteria (24) at visit 1 or (b) incident hospitalized heart failure (hospital discharge codes ICD-9 CM 428) before visit 4. Individuals who reported at visit 4 that a physician ever told them that they had cancer or lung disease represented those with prevalent cancer or respiratory disease, respectively.

Deaths from visit 4 (1996-98) through 2008 were identified through contacts with next of kin, searching hospital records and state death records, and linkage to the National Death Index. Cause- specific mortality was defined using the underlying cause of death on the death certificate (ICD-9 code or ICD-10 code). “All CVD deaths” were defined as death with ICD-9 code 401-459 or ICD-10 code I10-I99; “CHD deaths” were those with ICD-9

code 410-414 or ICD-10 code I20-I25; “stroke deaths”: ICD-9 code 430-438 or ICD-10 code I60-I69; “cancer deaths”: ICD-9 code 140-239 or ICD-10 code C00-D48 and “respiratory disease deaths”: ICD-9 code 460-519 or ICD-10 code J00- J98.

Statistical analysis

From the 11,668 who attended ARIC visit 4, we made exclusions as shown in Figure 1. For analyses of all CVD, CHD and stroke deaths, we excluded 1554 participants with prevalent CHD, stroke or heart failure at visit 4. We excluded 1200 participants with a history of cancer from cancer mortality analyses and 938 participants who had a known history of respiratory diseases from respiratory disease mortality analyses.

The association between the three biomarkers and mortality outcomes were determined with Cox proportional hazard models. We modeled Hs-TnT, Hs-CRP and NT-proBNP at visit 4 as both categorical and continuous variables. For Hs-TnT categorical analysis, the 31.7% with undetectable levels were the reference group. The remaining 68.3% were split into four groups : 0.003-0.005ug/L, 0.006-0.008ug/L, 0.009-0.013ug/L and ≥ 0.014ug/L, which corresponds to the 99th percentile value for Hs-TnT in a healthy subpopulation.(25) Hs-CRP and NT-proBNP were categorized as quintiles. The p for linear trend were determined by fitting a slope to biomarker categories. The distributions for Hs-TnT, NT-proBNP and Hs-CRP were right skewed and therefore were natural logarithm transformed for continuous analyses. Hazard ratios (HR) for continuous biomarkers were reported per standard deviation (SD) increment of the log-transformed biomarker.

Proportional hazard model 1 adjusted for age, sex and race. Model 2 adjusted for all components of model 1; body mass index, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diet, sport index, forced expiratory volume in 1 second, and estimated glomerular filtration rate as continuous variables; smoking status (current, former and never), drinking status (3 categories), hormone use (estrogen, estrogen and progestin, former and never), , antihypertensive medication (yes/no) and diabetes (yes/no) as categorical variables. Model 3 adjusted for all components of model 2 plus the other two biomarkers.

We tested two-way multiplicative interactions of each biomarker with race or sex and found none statistically significant at $p<0.10$, after Bonferroni correction for multiple interaction testing. Therefore, we pooled men and women, whites and African Americans for all final analyses. The proportional hazards assumption was tested by including time by biomarker interaction terms in the unadjusted models.

The Cox proportional hazard model was also used to assess the joint association with mortality of having zero, one, two, or three of the biomarkers elevated. The 80th percentile of each biomarker was used to dichotomize high and low.

RESULTS

As shown in Supplemental Tables 1-3, Hs-TnT, NT-proBNP, and Hs-CRP were associated with most risk factors at $p < 0.05$, given ARIC's large sample size. During a mean of 9.9 years follow up, there were 1909 total deaths, 358 all CVD deaths, 138 CHD deaths, 67 stroke deaths, 502 cancer deaths and 99 respiratory disease deaths (Figure 1).

As shown in Table 1, Hs-TnT was associated positively with risk of every cause-specific mortality outcome, after adjustment for CV risk factors (Model 2). Hazard ratios for the highest group versus the lowest in model 2 were: total mortality (HR: 3.42, 95% CI: 2.75-4.26), all CVD mortality (HR: 7.34, 95% CI: 4.64- 11.6), CHD mortality (HR: 6.06,

95% CI: 2.91-12.6), stroke mortality (HR: 3.31, 95% CI: 1.26-8.66), cancer mortality (HR: 1.60, 95% CI: 1.08- 2.38), and respiratory disease mortality (HR: 3.85, 95% CI: 1.39-10.7). The p value for trend for cancer mortality was not significant. Further adjustment for the other biomarkers (Model 3) somewhat attenuated the Hs-TnT associations, though they remained significant except for stroke mortality.

NT-proBNP groups were associated positively with total, all CVD, CHD, and stroke mortality (Table 2). Model 2 HRs for quintiles 5 versus 1 were: total (HR: 3.05, 95% CI: 2.46-3.77), all CVD (HR: 7.48, 95% CI: 4.67- 12.0), CHD (HR: 4.07, 95% CI: 2.07-7.98) and stroke mortality (HR: 10.4, 95%CI: 2.26-47.7). Associations were attenuated but remained significant after adjustment for the other two biomarkers (Model 3). In contrast, there was no significant association of NT-proBNP group with cancer or respiratory disease mortality after Model 2 adjustment.

As shown in Table 3, Hs-CRP levels in Model 2 were positively significantly associated with total mortality, all CVD mortality and respiratory disease mortality but not with CHD, stroke or cancer mortality when comparing quintile 5 versus 1. After adjustment for NT-proBNP and Hs-TnT (Model 3), greater Hs-CRP level was no longer associated with all-CVD mortality.

When we evaluated binary cutoffs in supplemental table 4-6 for each biomarker, the associations remained the same. However, the association of Hs-TnT and cancer mortality was now significant in Model 3.

The more markers elevated, the higher the cause specific mortality rate (Table 4). For example in Model 2, having all three of Hs-TnT, Hs-CRP and NT-proBNP elevated compared to having none carried a 5-fold increased risk of total mortality (HR: 4.31, 95% CI: 3.31-5.63), over a 10-fold risk of all CVD death (HR: 10.5, 95% CI: 6.38-17.3), a 6-fold risk of CHD mortality (HR: 6.18, 95% CI: 2.68- 14.3), a 12-fold risk of stroke mortality (HR: 12.0, 95% CI: 3.61-40.2) and a 5 fold risk of respiratory disease deaths (HR: 5.14, 95% CI: 1.61-16.4). Although the corresponding HRs was also elevated for cancer mortality (HR: 1.99, 95% CI: 1.00-3.98) this was not statistically significant. Notably, over 64% (i.e., 178/278) of those with all three biomarkers elevated died during the follow-up period.

There was some evidence that the proportional hazards assumption was violated for all three biomarkers for total mortality ($p<0.001$) and for NT-proBNP for CVD and CHD mortality ($p=0.01$). We therefore compared hazard ratios for the first and second halves of follow-up. For total mortality, associations with the three biomarkers tended to be stronger in later compared with earlier follow-up. The associations of NT-proBNP with CVD and CHD mortality tended to be stronger in earlier compared with later follow-up.

DISCUSSION

Our primary aim was to determine the association of Hs-TnT, NT-proBNP and Hs-CRP with cause-specific mortality in a population-based prospective study. The analyses after adjusting for cardiovascular risk factors suggest that all CVD and stroke mortality were associated most strongly with elevated NT-proBNP levels compared with Hs-TNT and Hs-CRP levels. The risk of CHD mortality was most strongly associated with elevated Hs-TNT, then NT-proBNP, and least for Hs-CRP. All three biomarkers showed only weak associations with cancer mortality. Our most novel finding may be that greater levels of Hs-TnT was associated with increased respiratory disease mortality. Risk of total, all CVD, CHD and stroke mortality were particularly elevated when all three biomarkers were elevated simultaneously, with over 60% of such participants dying during the follow up period.

The high sensitivity assay for TnT can detect a 10-fold lower concentration than detectable with the TnT conventional assay. With the high sensitivity TnT assay, approximately 25-67% of adults from the general population have detectable troponin levels.(1-3) In a study by Daniels et al, TnT was detectable in 4% of apparently healthy participants using a conventional assay, and they were at increased risk of all-cause and cardiovascular death. (26) The low prevalence of detection with conventional assays limited the utility of troponin measurement for predicting future cardiovascular disease.(3) Although there are few direct comparisons made between the conventional and high sensitivity assays,(15,27) Hs-TnT seems to increase the predictive power of troponin measurement. The Cardiovascular Health Study and Dallas Heart Study have shown greater levels of Hs-TnT are associated with incident cardiovascular events and all-cause or cardiovascular mortality;(1-3,26). ARIC showed similar association with incident cardiovascular events and all-cause mortality.(1) We now extend these findings to mortality from CVD in ARIC, CHD, stroke, and respiratory disease. The strong association of low detectable troponin T with all CVD and CHD mortality is consistent with the presence of subclinical chronic myocardial injury causing increased risk of death.(28-30) Recent studies have suggested that the association of TnT levels with cardiac outcomes in previously asymptomatic individuals may be mediated through mechanisms independent of atherosclerosis.(1) Though these mechanisms remain unclear, cardiac myocytes may release troponin T due to asymptomatic ischemia, coronary microvascular dysfunction, apoptosis, or subclinical cardiac structural or functional abnormalities. In addition, the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial revealed that Hs-TnT was associated with heart failure and death but not myocardial infarction in patients with chronic coronary artery disease.(31) However, the Heart Outcomes Prevention Evaluation study (HOPE) showed association of high sensitivity Troponin I with myocardial infarction in a high risk population. (32)

It is of interest that elevated Hs-TnT is associated with increased respiratory disease mortality especially if troponin is released as a result of myocardial damage. In our analyses, patients with chronic obstructive pulmonary disease (COPD) may have had CHD (33) or acute exacerbations of COPD may cause subclinical myocardial damage via right ventricular overload. Also COPD could lead to hypoxia and tachycardia, which could affect cardiac oxygen demand, and delivery, causing myocardial ischemia which may cause release of TnT.(34) A recent study has shown that elevated Hs-TnT during acute exacerbation of COPD is more frequent among patients with tachycardia than among those with normal heart rate, and this is associated with decreased survival.(34)

Brain natriuretic peptide (BNP) is synthesized as an inactive pro-hormone primarily from the cardiac ventricles as a result of myocardial wall stress, it splits into an active BNP and inactive but stable NT-proBNP. They both serve as biomarkers for diagnosis, prognosis, and management in patients with cardiovascular disease and heart failure.(7,35) In this study, greater levels of NT-proBNP were positively associated with total mortality, all CVD mortality, CHD and stroke mortality. The Framingham Heart Study (FHS), Prevention of Renal and Vascular End-stage Disease (PREVEND) study and two other European studies, have documented a positive association of plasma B type natriuretic peptide with cardiovascular events and all-cause mortality.(36-40) Linssen et al reported NT-proBNP is associated crudely with non-CVD mortality, but not after adjustment for risk factors, as seen in our analysis for cancer and respiratory disease mortality.(36) Elevated NT-proBNP levels in the general population may reflect the presence of structural heart disease or cardiac remodeling resulting from increased cardiac stretch from pressure or volume overload, (15,36,41) or they also may reflect coronary atherosclerosis.(42-45)

Our finding of NT-proBNP associated with stroke mortality might be explained by strokes from cardio-embolic causes, such as atrial fibrillation, and concomitant NT-proBNP

elevation.(46) Immunochemical studies also have suggested that cerebral ischemia induces natriuretic peptide secretion in brain tissue;(47) elevated BNP levels are not uncommon in acute stroke and are associated with reduced survival.(48) Cerebral ischemia and neurologic deficits have been found to be associated with high concentration of plasma BNP, and occult cardiac dysfunction increases the risk of severe strokes in patients.(48) Although the association of NT-proBNP with stroke mortality was statistically significant, the confidence interval of the HR estimates was wide due relatively few stroke deaths. Therefore, larger investigations may be needed to address the relation of NT-proBNP and stroke incidence and mortality.

Since Hs-CRP serves as a sensitive but nonspecific marker of systemic inflammation,(10) it is not surprising that we found CRP associated with multiple mortality outcomes, because inflammation plays a major role in the pathophysiology of the disease related mortality. The Emerging Risk Factors Collaboration carried out a meta-analysis assessing the association of Hs-CRP with vascular and non-vascular mortality in people without a history of vascular disease from long-term prospective studies (ARIC included).(12) Every three-fold higher increment of CRP approximately doubled risk of all vascular, non-vascular, cancer and respiratory disease deaths, after adjustment for age and sex.(12) The significant association of Hs-CRP and CVD mortality was lost after adjusting for the other two biomarkers. This may also question the need of CRP as a predictor of future cardiovascular events.

Individuals with cancer often die from infection, respiratory failure, cardiovascular insufficiency, hemorrhagic and thromboembolic phenomena,(49) which could possibly be related to the effects of treatment-surgery(50) or chemotherapy.(51) Some of these conditions are associated with elevated TnT(51), which could possibly explain a weak association with cancer mortality. Although CRP is an inflammatory marker, there is still limited and less consistent evidence of its association with cancer.(52)

The strengths of our study include the large cohort of middle aged to older adults, and the use of highly sensitive assays. We studied mortality because information relating TnT and NT-proBNP to cause-specific mortality was limited, and it is useful to know if these cardiac biomarkers only relate to cardiovascular causes of death or whether they relate non-specifically to other causes. There are some drawbacks to our study. We did not perform a validation study for causes of death but rather used the ICD code for underlying cause. We had only a single assessment of biomarkers at the beginning of follow-up, and changes likely would have occurred during follow-up. We excluded individuals who were initially free of the disease whose mortality was being studied, but many people likely had co-morbid conditions, often subclinical, that contributed to death over the next decade. A final drawback of our study was that, despite its size, the numbers of stroke and respiratory deaths were modest.

In summary, greater levels of Hs-TnT, NT-proBNP and Hs-CRP are associated with increased risk of death, not just from cardiovascular disease but also from some non-cardiovascular causes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation and Acronym

Hs-TnT	High sensitivity Troponin T
NT-proBNP	N-terminal pro-brain natriuretic peptide
Hs-CRP	High sensitivity C-reactive protein
ARIC	Atherosclerosis Risk in Communities
CVD	Cardiovascular disease
CHD	Coronary heart disease
eGFR	Estimated glomerular filtration rate
FEV1	Forced expiratory volume in 1 second
MS	Mississippi
MN	Minnesota
NC	North Carolina
MD	Maryland
MI	Myocardial infarction
HF	Heart failure
HR	Hazard ratio
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition
COPD	Chronic obstructive pulmonary disease
FHS	Framingham Heart Study
PREVEND	Prevention of Renal and Vascular End-stage Disease
HOPE	Heart Outcomes Prevention Evaluation

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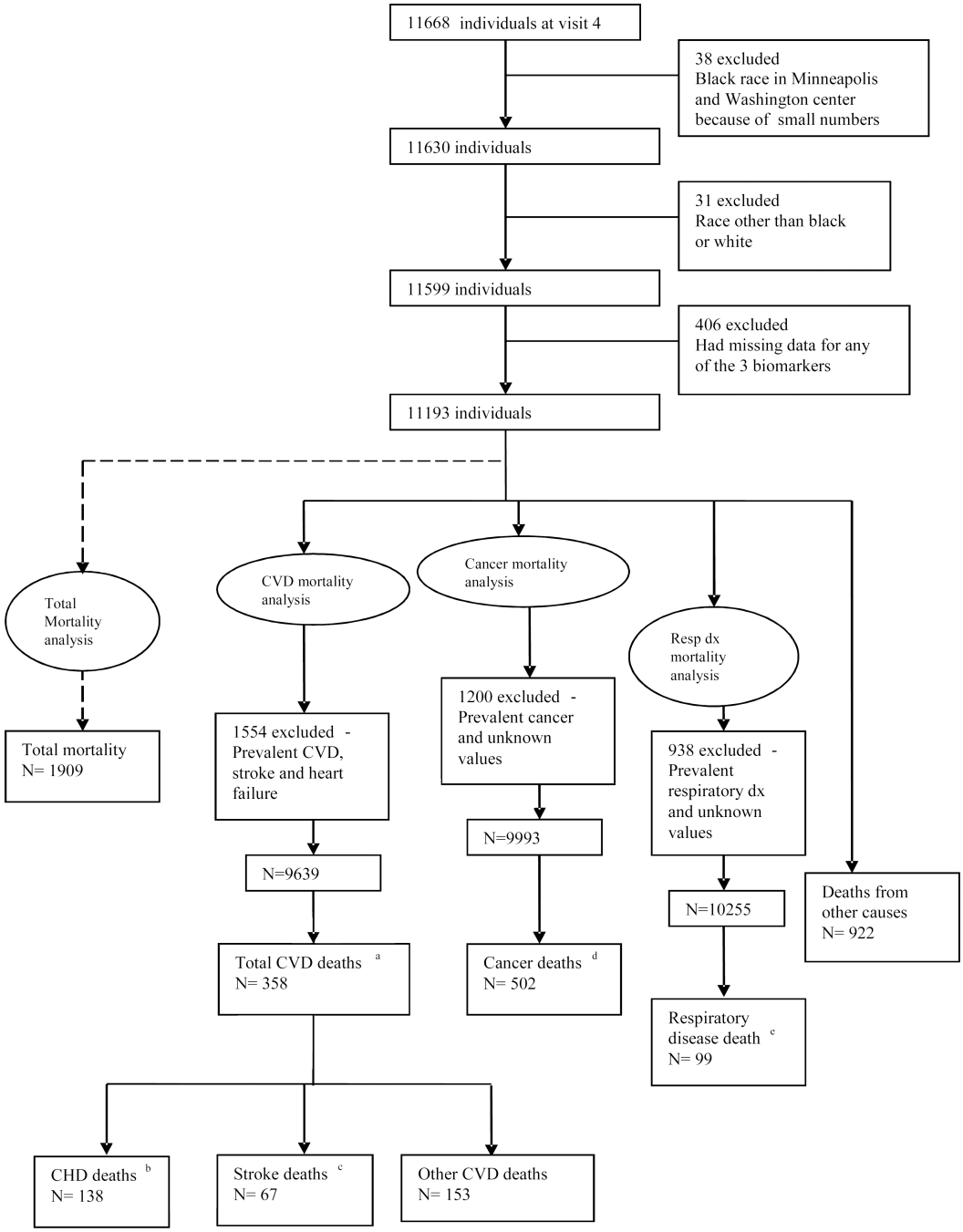

Figure 1.
Participant Flow Chart
[a] Total Cardiovascular disease deaths: ICD 9 code 401- 459 or ICD-10 code I10- I99
[b] Coronary Heart disease deaths: ICD 9 code 410- 414 or ICD-10 code I20- I25
[c] Stroke deaths: ICD 9 code 430- 438 or ICD-10 code I60- I69
[d] Cancer deaths: ICD 9 code 140- 239 or ICD-10 code C00- D48

Table 1

Hazard Ratios for associations between Troponin T and mortality, ARIC, 1996-2008

	Hazard ratio (95% Confidence Interval)					
	<3ng/L	**3- ≤5ng/L**	**6-≤ 8ng/L**	**9- ≤13ng/L**	**≥14ng/L**	***P* for trend**
N	3544	2779	2269	1535	1066	
Total mortality (n=1909) Events	306	349	359	394	501	
Model 1	1	1.26 (1.07- 1.47)	1.37 (1.16- 1.61)	2.02 (1.71- 2.38)	4.34 (3.68- 5.12)	<0.0001
Model 2	1	1.38 (1.13- 1.67)	1.53 (1.25- 1.86)	1.91 (1.55- 2.35)	3.42 (2.75- 4.26)	<0.0001
Model 3	1	1.32 (1.09- 1.61)	1.42 (1.16- 1.74)	1.73 (1.40- 2.13)	2.82 (2.26- 3.53)	<0.0001
All CVD mortality (n=358) Events	51	63	64	77	103	
Model 1	1	1.42 (0.98- 2.07)	1.67 (1.14- 2.44)	2.88 (1.97- 4.20)	7.71 (5.31- 11.2)	<0.0001
Model 2	1	1.50 (0.96- 2.36)	1.89 (1.20- 2.97)	3.01 (1.91- 4.75)	7.34 (4.64- 11.6)	<0.0001
Model 3	1	1.41 (0.90- 2.22)	1.70 (1.08- 2.66)	2.54 (1.60- 4.01)	5.09 (3.18- 8.15)	<0.0001
CHD mortality (n= 138) Events	19	24	30	28	37	
Model 1	1	1.37 (0.74- 2.51)	1.89 (1.04- 3.43)	2.42 (1.29- 4.51)	6.22 (3.37- 11.5)	<0.0001
Model 2	1	1.28 (0.61- 2.68)	2.17 (1.09- 4.35)	2.42 (1.16- 5.06)	6.06 (2.91- 12.6)	<0.0001
Model 3	1	1.25 (0.60- 2.63)	2.03 (1.01- 4.07)	2.22 (1.06- 4.64)	4.65 (2.19- 9.89)	<0.0001
Stroke mortality (n= 67) Events	17	15	5	14	16	
Model 1	1	0.98 (0.48- 1.97)	0.38 (0.14- 1.06)	1.53 (0.71- 3.32)	3.87 (1.78- 8.41)	0.003
Model 2	1	1.00 (0.43- 2.29)	0.31 (0.09- 1.14)	1.89 (0.78- 4.58)	3.31 (1.26- 8.66)	0.02
Model 3	1	0.91 (0.39- 2.09)	0.28 (0.08- 1.02)	1.57 (0.64- 3.85)	2.34 (0.86- 6.33)	0.09
Cancer Mortality (n= 502) Events	127	119	105	81	70	
Model 1	1	0.99 (0.76- 1.28)	0.87 (0.66- 1.14)	0.90 (0.66-1.23)	1.28 (0.91- 1.80)	0.60
Model 2	1	1.15 (0.85- 1.54)	1.04 (0.75- 1.43)	1.02 (0.71- 1.46)	1.60 (1.08- 2.38)	0.17
Model 3	1	1.14 (0.84- 1.53)	1.02 (0.74- 1.41)	0.99 (0.69- 1.43)	1.52 (1.01- 2.28)	0.27
Respiratory disease mortality (n= 99) Events	15	14	24	23	23	
Model 1	1	0.91 (0.43- 1.95)	1.69 (0.85- 3.38)	2.11 (1.02- 4.35)	3.84 (1.82- 8.10)	<0.0001
Model 2	1	1.15 (0.42- 3.12)	2.34 (0.94- 5.78)	2.48 (0.96- 6.45)	3.85 (1.39- 10.7)	0.004
Model 3	1	1.12 (0.41- 3.03)	2.26 (0.91- 5.62)	2.48 (0.95- 6.51)	3.80 (1.35- 10.7)	0.004

CHD- indicates coronary heart disease, CVD- indicates cardiovascular disease, *P* for linear trend across categories

Model 1- adjusted for age, sex and race

Model 2- adjusted for model 1 + body mass index, total cholesterol, high density lipoprotein cholesterol, diet, sport index, smoking status, drinking status, hormone use, systolic blood pressure, antihypertensive medication, diabetes, forced expiratory volume in 1 second/forced vital capacity predicted %, estimated glomerular filtration rate. In addition, total mortality was adjusted for history of cancer, CVD, stroke, heart failure and respiratory disease

Model 3- adjusted for model 2 + high sensitivity C- reactive protein (Hs-CRP) and N terminal pro B natriuretic peptide (NT-proBNP)

Table 2

Hazard Ratios for associations between N Terminal pro-B natriuretic peptide and mortality, ARIC, 1996-2008

	Hazard ratio (95% Confidence Interval)					
	≤ 27.4pg/ml	**27.5-52.3pg/ml**	**52.4-88.6pg/ml**	**88.7-158.0pg/ml**	**≥159pg/ml**	***P* for trend**
N	2240	2244	2239	2233	2237	
Total mortality (n=1909) Events	208	256	342	350	753	
Model 1	1	1.28 (1.06- 1.55)	1.80 (1.51- 2.16)	1.92 (1.60- 2.30)	3.87 (3.27- 4.58)	<0.0001
Model 2	1	1.33 (1.07- 1.65)	1.78 (1.43- 2.20)	1.92 (1.55- 2.38)	3.05 (2.46- 3.77)	<0.0001
Model 3	1	1.26 (1.01- 1.57)	1.63 (1.32- 2.02)	1.74 (1.40- 2.16)	2.46 (1.98- 3.05)	<0.0001
All CVD mortality (n= 358) Events	33	51	67	62	145	
Model 1	1	1.77 (1.14- 2.75)	2.57 (1.68- 3.93)	2.70 (1.75- 4.18)	7.33 (4.92- 10.9)	<0.0001
Model 2	1	1.99 (1.20- 3.29)	3.03 (1.87- 4.92)	2.77 (1.67- 4.60)	7.48 (4.67- 12.0)	<0.0001
Model 3	1	1.81 (1.09- 2.99)	2.55 (1.57- 4.14)	2.27 (1.37- 3.78)	5.10 (3.16- 8.22)	<0.0001
CHD mortality (n= 138) Events	18	25	28	15	52	
Model 1	1	1.52 (0.82- 2.80)	1.86 (1.01- 3.42)	1.12 (0.55- 2.27)	4.44 (2.50- 7.88)	<0.0001
Model 2	1	1.55 (0.78- 3.11)	2.01 (1.02- 3.98)	1.11 (0.49- 2.47)	4.07 (2.07- 7.98)	0.0002
Model 3	1	1.43 (0.71- 2.86)	1.73 (0.87- 3.43)	0.93 (0.41- 2.07)	2.81 (1.41- 5.60)	0.01
Stroke mortality (n= 67) Events	3	9	13	13	29	
Model 1	1	2.95 (0.79- 11.0)	4.38 (1.23- 15.6)	4.64 (1.29- 16.7)	12.0 (3.52- 41.1)	<0.0001
Model 2	1	3.87 (0.81- 18.4)	5.91 (1.29- 27.1)	4.50 (0.93- 21.8)	10.4 (2.26- 47.7)	0.001
Model 3	1	3.61 (0.76- 17.2)	5.34 (1.17- 24.5)	4.02 (0.83- 19.5)	7.76 (1.67- 36.2)	0.01
Cancer Mortality (n= 502) Events	86	98	103	99	116	
Model 1	1	1.13 (0.84- 1.52)	1.24 (0.92- 1.68)	1.20 (0.88- 1.63)	1.41 (1.04- 1.93)	0.04
Model 2	1	1.13 (0.82- 1.56)	1.21 (0.87- 1.70)	1.25 (0.89- 1.76)	1.39 (0.97- 2.00)	0.07
Model 3	1	1.12 (0.81- 1.55)	1.19 (0.85- 1.66)	1.22 (0.86- 1.72)	1.30 (0.90- 1.88)	0.16
Respiratory disease mortality (n= 99) Events	8	13	24	23	31	
Model 1	1	1.52 (0.62- 3.68)	2.98 (1.32- 6.77)	2.78 (1.20- 6.44)	3.36 (1.46- 7.72)	0.001
Model 2	1	1.48 (0.49- 4.48)	2.45 (0.86- 7.04)	2.99 (1.05- 8.49)	2.02 (0.67- 6.09)	0.12
Model 3	1	1.33 (0.44- 4.06)	2.15 (0.75- 6.17)	2.59 (0.91- 7.38)	1.45 (0.48- 4.43)	0.37

CHD- indicates coronary heart disease, CVD- indicates cardiovascular disease, *P* for linear trend across quintiles

Model 1- adjusted for age, sex and race

Model 2- adjusted for model 1 + body mass index, total cholesterol, high density lipoprotein cholesterol, diet, sport index, smoking status, drinking status, hormone use, systolic blood pressure, antihypertensive medication, diabetes, forced expiratory volume in 1 second/forced vital capacity predicted %, estimated glomerular filtration rate. In addition, total mortality was adjusted for history of cancer, CVD, stroke, heart failure and respiratory disease

Model 3- adjusted for model 2 + high sensitivity C- reactive protein (Hs-CRP) and troponin T

Table 3

Hazard Ratios for associations between C reactive protein and mortality, ARIC, 1996-2008

	Hazard ratio (95% Confidence Interval)					
	≤0.9mg/L	**0.917-1.761 mg/L**	**1.762-3.389mg/L**	**3.390-6.578mg/L**	**≥6.579mg/L**	***P* for trend**
N	2238	2239	2239	2239	2238	
Total mortality (n=1909) Events	302	328	331	430	518	
Model 1	1	1.07 (0.91- 1.26)	1.13 (0.96- 1.32)	1.63 (1.40- 1.90)	2.14 (1.84- 2.49)	<0.0001
Model 2	1	1.05 (0.87- 1.27)	1.14 (0.94- 1.38)	1.48 (1.22- 1.79)	1.61 (1.32- 1.97)	<0.0001
Model 3	1	1.07 (0.88- 1.29)	1.12 (0.93- 1.36)	1.40 (1.16- 1.70)	1.46 (1.20- 1.78)	<0.0001
All CVD mortality (n= 358) Events	62	68	50	77	101	
Model 1	1	1.12 (0.79- 1.58)	0.85 (0.59- 1.24)	1.44 (1.03- 2.02)	2.09 (1.51- 2.90)	<0.0001
Model 2	1	1.07 (0.73- 1.59)	0.85 (0.56- 1.30)	1.26 (0.85- 1.88)	1.76 (1.19- 2.62)	0.004
Model 3	1	1.11 (0.75- 1.65)	0.85 (0.56- 1.31)	1.15 (0.77- 1.72)	1.49 (1.00- 2.21)	0.06
CHD mortality (n= 138) Events	21	25	20	36	36	
Model 1	1	1.22 (0.68- 2.18)	1.03 (0.56- 1.90)	2.10 (1.22- 3.62)	2.43 (1.40- 4.22)	0.0002
Model 2	1	1.08 (0.57- 2.03)	0.98 (0.50- 1.91)	1.66 (0.89- 3.09)	1.88 (0.98- 3.59)	0.02
Model 3	1	1.12 (0.59- 2.12)	0.98 (0.50- 1.91)	1.52 (0.81- 2.84)	1.66 (0.87- 3.18)	0.08
Stroke mortality (n= 67) Events	16	14	9	8	20	
Model 1	1	0.88 (0.43- 1.80)	0.58 (0.26- 1.32)	0.56 (0.24- 1.31)	1.58 (0.80- 3.12)	0.45
Model 2	1	1.17 (0.50- 2.74)	0.90 (0.35- 2.31)	0.90 (0.33- 2.44)	2.24 (0.90- 5.53)	0.21
Model 3	1	1.15 (0.49- 2.73)	0.93 (0.36- 2.38)	0.85 (0.31- 2.34)	1.91 (0.77- 4.71)	0.33
Cancer Mortality (n= 502) Events	82	99	103	110	108	
Model 1	1	1.23 (0.92- 1.66)	1.35 (1.01- 1.82)	1.61 (1.20- 2.16)	1.72 (1.27- 2.33)	<0.0001
Model 2	1	1.12 (0.81- 1.56)	1.31 (0.94- 1.81)	1.35 (0.96- 1.91)	1.38 (0.95- 2.00)	0.05
Model 3	1	1.14 (0.82- 1.59)	1.31 (0.94- 1.82)	1.34 (0.95- 1.89)	1.35 (0.93- 1.96)	0.07
Respiratory disease mortality (n= 99) Events	14	15	15	20	35	
Model 1	1	1.01 (0.47- 2.19)	1.20 (0.56- 2.56)	2.02 (1.00- 4.07)	4.01 (2.08- 7.73)	<0.0001
Model 2	1	1.57 (0.63- 3.87)	1.34 (0.52- 3.45)	2.08 (0.83- 5.22)	3.36 (1.34- 8.45)	0.01
Model 3	1	1.65 (0.66- 4.11)	1.41 (0.54- 3.66)	2.09 (0.83- 5.26)	3.38 (1.34- 8.50)	0.01

CHD- indicates coronary heart disease, CVD- indicates cardiovascular disease, *P* for linear trend across quintiles

Model 1- adjusted for age, sex and race

Model 2- adjusted for model 1 + body mass index, total cholesterol, high density lipoprotein cholesterol, diet, sport index, smoking status, drinking status, hormone use, systolic blood pressure, antihypertensive medication, diabetes, forced expiratory volume in 1 second/forced vital capacity predicted %, estimated glomerular filtration rate. In addition, total mortality was adjusted for history of cancer, CVD, stroke, heart failure and respiratory disease

Model 3- adjusted for model 2 + troponin T and N terminal pro B natriuretic peptide (NT-proBNP)

Table 4

Hazard Ratios for Joint associations of elevated Troponin T, NT-proB natriuretic peptide, or C reactive protein with mortality, ARIC 1996-2008

	Hazard ratio (95% Confidence Interval) according to number elevated [a]			
	0	**1**	**2**	**3**
N	5899	3789	1227	278
Total mortality (n=1909)	569	692	470	178
Model 2	1	1.50 (1.31- 1.72)	2.31 (1.94- 2.74)	4.31 (3.31- 5.63)
All CVD mortality (n=358)	93	135	99	31
Model 2	1	2.06 (1.51- 2.81)	5.12 (3.61- 7.25)	10.5 (6.38- 17.3)
CHD mortality (n= 138)	44	44	41	9
Model 2	1	1.22 (0.75- 1.99)	4.11 (2.45- 6.90)	6.18 (2.68- 14.3)
Stroke mortality (n=67)	19	25	15	8
Model 2	1	2.09 (1.04- 4.22)	4.87 (2.18- 10.9)	12.0 (3.61- 40.2)
Cancer Mortality (n= 502)	227	194	62	19
Model 2	1	1.13 (0.90- 1.42)	1.14 (0.80- 1.63)	1.99 (1.00- 3.98)
Respiratory disease mortality (n= 99)	28	41	19	11
Model 2	1	1.27 (0.69- 2.34)	1.70 (0.78- 3.74)	5.14 (1.61- 16.4)

CHD- indicates coronary heart disease, CVD- indicates cardiovascular disease, model 1- adjusted for age, sex and race

Adjusted for model 1+ body mass index, total cholesterol, high density lipoprotein cholesterol, diet, sport index, smoking status, drinking status, hormone use, systolic blood pressure, antihypertensive medication, diabetes, forced expiratory volume in 1 second/forced vital capacity predicted %, estimated glomerular filtration rate. In addition, total mortality was adjusted for history of cancer, CVD, stroke, heart failure and respiratory disease

[a] elevated was defined by being above versus below the 80th percentile for each biomarker