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Serum Resistin Concentrations and Incident Heart Failure in Older Adults

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Global Epidemiology

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Serum Resistin Concentrations and Incident Heart Failure in Older Adults

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Bachelor of Science

Central South University

2008

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Abstract

Serum Resistin Concentrations and Incident Heart Failure in Older Adults

By Zhaochuan Wang

Objectives: Resistin is a polypeptide found in adipocytes that promotes insulin resistance and may be a novel risk factor for heart failure. We investigated the association between baseline serum resistin concentrations and incident heart failure (HF) during the next 5 years for adults aged 70-79 years.

Methods: We used data from the Health, Aging, and Body Composition (Health ABC) Study, a prospective, NIH-funded cohort study, which enrolled 3075 participants from Pittsburg, PA, and Memphis, TN. Kaplan-Meier survival curves were plotted for incident HF during the 5-year follow up by resistin quartiles, overall and in subgroups by race and gender. The Cochran-Armitage trend test was used to compare incident HF across quartiles of baseline serum resistin concentrations. Cox proportional hazards model was used to assess whether baseline serum resistin concentration was associated with incident HF over 5 years of follow up. Assessment of interaction and confounding was performed.

Results: Median follow-up time was 949 days. Incident HF curves were significantly different among resistin quartile groups (log-rank test p-value < 0.0001). The lowest quartile of serum resistin had the highest probability of HF-free survival, followed by 2^{nd}, 3^{rd} quartiles, and lastly the 4^{th} quartile. Serum resistin concentration was associated with incident HF during the follow-up period [raw HR per 10 ng/ml increase = 1.21 (95% CI: 1.16-1.27), p=0.005;]. The multivariable adjusted effect of resistin HR per 10 ng/ml increase in the overall population is 1.13 (95% CI: 1.11-1.15, p=0.14). This association was modified by baseline physical activity status (p-value for interaction= 0.0438). The hazard of incident HF was 1.21 (95% CI: 1.19-1.23, p=0.006) and 1.22 (95% CI: 1.21-1.24, p=0.004) per 10 ng/ml increase in serum resistin level for participants with physical activity and physical inactivity respectively. This effect of resistin on incident HF was also confounded by sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and baseline serum albumin concentration.

Conclusions: Serum resistin concentration is associated with incident HF over 5 years in older adults, and this association was modified by physical activity and confounded by sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and baseline serum albumin concentration.

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Chapter 1

Literature Review

Heart Failure

Heart failure (HF), often called congestive heart failure, occurs when the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body. Heart failure can cause a number of symptoms including shortness of breath, leg swelling, and exercise intolerance. The condition is diagnosed by patient physical examination and confirmed with echocardiography (1).

Heart failure is a common health problem, which has a poor prognosis with high mortality rate and its incidence has increased continuously in the past decade (2). In the USA, HF affects about 5.1 million adults older than 20 years of age with 550,000 cases per year (3). The American Heart Association (AHA) also estimates that by 2030, the prevalence of HF will increase 25% (4). The onset of HF is uneven across age, race and gender (4). Among people over 65 years of age, the HF incidence approaches 10 per 1000, and shows a increasing trend with the effect being greater in men. Seventy-five percent of HF cases have antecedent hypertension (5,6). The annual risks per 1000 population of new HF events for white men are 15.2 for those 65 to 74 years of age, 31.7 for those 75 to 84 years of age, and 65.2 for those ≥85 years of age. For white women in the same age groups, the risks are 8.2, 19.8, and 45.6, respectively. For black men, the risks are 16.9, 25.5, and 50.6, and for black women, the estimated risks are 14.2, 25.5, and 44.0, respectively (7). Compared to other ethnic groups, African Americans have the highest risk of developing HF, followed by Hispanic, Caucasian, and Chinese Americans,

according to the Multi-Ethnic Study of Atherosclerosis (MESA) study, which reported ethnic differences in the prevalence of hypertension, obesity, diabetic, systolic dysfunction and socioeconomic status (8,9).

There are over 1 million hospitalizations annually for HF, 1.8 millions physician office visits with a primary diagnosis of HF in 2010, 668,000 emergency room visits and 293, 000 outpatient department visits for HF in 2009 in the U.S (10). HF patients have a poor quality of life and shorter life expectancy and also impose a heavy financial burden to the health care system. Re-admission risk post discharge is approximately 50% within 6 months of hospitalization. The AHA estimated that the total cost of HF would increase almost 120% to $70 billion in 2030 based on the 2013 estimated total cost of $32 billion (11).

Since the initiation of the Framingham Heart Study, the survival time after HF onset has increased but the mortality rate is still as high as 50% after HF diagnosis within 5 years (12, 13).

The overall 1-year mortality rate declined slightly over the past decade but remains high. Changes were uneven across states among Medicare beneficiaries (14).

Risk Factors for Heart Failure

Because of the high mortality associated with HF and an aging population, it is very important to identify risk factors for HF in order to evaluate prevention strategies. Under these circumstances, a large number of risk factors have been studied and established.

In the Framingham Heart Study, age, coronary heart disease (CHD), valvular heart disease (VHD), left ventricular hypertrophy, diabetes, and obesity were associated with an increasing risk of HF (13). B-type natriuretic peptide, urinary albumin-to-creatinine ratio, and elevated serum γ-glutamyl transferase were also established as risk factors (15, 16).

Cigarette smoking was identified as an important and independent risk factor. There was a 45% higher risk of HF in men and 88% higher risk in women among smokers after adjusting for CHD and other known risk factors for HF (17). Physical inactivity and lower socioeconomic status were also considered as important and independent risk factors in prospective cohort studies (17). Although a higher level of physical activity was associated with CHD, hypertension, obesity and diabetes, after adjusting for these established factors, physical inactivity also attributed to 9.2% of HF cases in US general population, which indicated a higher physical activity leads to a lower risk of HF. Lower educational level is associated with low access to healthcare which is an important risk factor on HF (17).

Hypertension, healthy lifestyle (normal weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were researched in the Physicians Health Study, which showed that hypertension was a risk factor for HF and a healthy lifestyle was related to lower risk of HF (18).

Serum resistin has been recently identified as a potential risk marker and risk factor for HF. Higher concentrations of resistin in serum were found in subjects with prevalent HF (19). In the Framingham Offspring Study, resistin was found to be strongly

associated with increased risk of HF during 6 years of follow-up of a community-based sample. This association persisted after adjusting for obesity, markers of insulin resistance, inflammation, concentrations of B-type natriuretic peptide, and other established HF risk factors (12).

Resistin

Resistin is a 114-amino acid (12.5 kDa) signaling polypeptide found in adipocytes that got its name because it seems to cause insulin resistance. This protein was also demonstrated to impair insulin action in normal mice and cultured adipocytes, and immunoneutralization of resistin improved insulin action in mice with diet-induced obesity. Insulin-stimulated glucose uptake was also increased by resistin neutralization and was reduced by resistin treatment (20).

Resistin was also found in other types of cells like macrophages and was associated with inflammation (21-23). Several studies showed that serum Resistin correlate with the risk for CHD, renal dysfunction and outcomes among stroke patients (23-26).

Resistin levels are also altered by thiazolidinediones (TZDs), a class of insulin sensitizing drugs that suppress resistin expression in 3T3-L1 adipocytes and in white adipose tissues of mice fed a high fat diet (27).

Increased serum resistin level was observed in the serum of obese and type 2 diabetic patients (28, 29). These elevations suggesting resistin may play an important role in the etiology of insulin resistance and diabetes. Resistin was also observed to impair glucose transport in isolated cardiomyocytes, suggesting resistin may affect cardiac

function. However, the exact pathophysiology has not yet been clearly elucidated and the underlying mechanism by which resistin impairs cardiac function is unknown (30).

Relationship between Resistin and Heart Failure

Several prospective cohort studies have shown that resistin was associated with prevalent HF or HF incidence (12, 17, 31). The mechanisms may involve insulin resistance, inflammation and effects on cardiomyocytes.

Glucose homeostasis and insulin action was affected after resistin protein was administered intraperitoneally in mice (20). It was also demonstrated that in skeletal muscle cells and adipocytes, the recombinant resistin impaired glucose transport in primary mouse cardiomyocytes. This evidence indicated a potential relationship between resistin and glucose metabolism related HF (20, 32, 33).

It was demonstrated that several markers of inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) receptor 2 and plasminogen activator inhibitor-1, had been associated with HF, and these biomarkers also correlated with elevated serum resistin level (34, 35). These inflammatory and fibrinolytic markers were also demonstrated to have a strong association with insulin resistance and metabolic syndrome as well (36).

Resistin also may influence HF onset by direct mechanisms on cardiomyocytes. Studies have demonstrated that over-expression of resistin in neonatal rats could cause an increase in sarcomere organization, protein synthesis in cardiomyocytes, and altered myocyte mechanics by depressing cell contractility and relaxation velocities. Resistin could also stimulate TNF-α secretion and impair cardiac recovery after ischemia occurred which plays an interesting role in myocardial damage and HF (37, 38).

Chapter 2

Manuscript

Abstract

Serum Resistin Concentrations and Incident Heart Failure in Older Adults

By Zhaochuan Wang

Objectives: Resistin is a polypeptide found in adipocytes that promotes insulin resistance and may be a novel risk factor for heart failure. We investigated the association between baseline serum resistin concentrations and incident heart failure (HF) during the next 5 years for adults aged 70-79 years.

Methods: We used data from the Health, Aging, and Body Composition (Health ABC) Study, a prospective, NIH-funded cohort study, which enrolled 3075 participants from Pittsburg, PA, and Memphis, TN. Kaplan-Meier survival curves were plotted for incident HF during the 5-year follow up by resistin quartiles, overall and in subgroups by race and gender. The Cochran-Armitage trend test was used to compare incident HF across quartiles of baseline serum resistin concentrations. Cox proportional hazards model was used to assess whether baseline serum resistin concentration was associated with incident HF over 5 years of follow up. Assessment of interaction and confounding was performed.

Results: Median follow-up time was 949 days. Incident HF curves were significantly different among resistin quartile groups (log-rank test p-value < 0.0001). The lowest quartile of serum resistin had the highest probability of HF-free survival, followed by 2^{nd}, 3^{rd} quartiles, and lastly the 4^{th} quartile. Serum resistin concentration was associated with incident HF during the follow-up period [raw HR per 10 ng/ml increase = 1.21 (95% CI: 1.16-1.27), p=0.005;]. The multivariable adjusted effect of resistin HR per 10 ng/ml increase in the overall population is 1.13 (95% CI: 1.11-1.15, p=0.14). This association was modified by baseline physical activity status (p-value for interaction= 0.0438). The hazard of incident HF was 1.21 (95% CI: 1.19-1.23, p=0.006) and 1.22 (95% CI: 1.21-1.24, p=0.004) per 10 ng/ml increase in serum resistin level for participants with physical activity and physical inactivity respectively. This effect of resistin on incident HF was also confounded by sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and baseline serum albumin concentration.

Conclusions: Serum resistin concentration is associated with incident HF over 5 years in older adults, and this association was modified by physical activity and confounded by sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and baseline serum albumin concentration.

1 INTRODUCTION

1.1 Background

Heart failure (HF) is a common health problem that has a poor prognosis with high mortality rate (2). In the USA, HF affects about 5.1 million adults based on the data collected by National Health and Nutrition Examination Survey, with an incidence of 550,000 cases per year (5).

Because of the high population prevalence of HF and increasingly older population, it is very important to identify the risk factors in order to prepare the preventative strategy. Under this circumstance, a large number of risk factors had been studied and established including age, CHD, hypertension, Valvular heart disease (VHD), left ventricular hypertrophy, diabetes, obesity, cigarette smoking, physical inactivity, lower socioeconomic status, and unhealthy lifestyle (10-12).

Serum resistin may be a novel risk factor for HF. Higher serum concentrations of resistin were found in subjects with prevalent HF (19). The mechanisms may involve insulin resistance, inflammation and effects on cardiomyocytes (12, 20, 37, 38).

1.2 Objectives

The research objective was to assess the association between baseline serum resistin concentration and incident HF during 5 years of follow-up for the elderly population aged 70-79 years.

2 METHODOLOGY

2.1 Study population and data collection

Data for this analysis are from the Health, Aging, and Body Composition (Health ABC) Study, a prospective cohort study investigating the associations among body composition, weight-related health conditions, and incident functional limitation in older adults. The Health ABC Study enrolled 3075 community dwelling black and white men and women aged 70 –79 years between April 1997 and June 1998. Participants were recruited from a random sample of white Medicare-eligible residents and all of the black Medicare-eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Subjects were eligible if they reported no difficulty walking one-fourth of a mile, climbing up 10 steps, or performing basic activities of daily living; were free of life-threatening illness; planned to remain in the geographic area for ≥3 y; and were not enrolled in lifestyle intervention trials. All participants provided written informed consent. The Institutional Review Boards at both sites approved the protocol (35).

At baseline a total of 3075 eligible participants were identified from the original cohort, participants with HF or missing data on HF were excluded. Among participants without prevalent HF, 2905 (99.0%) had available serum resistin concentrations. Participants with missing or extreme values of serum resistin concentrations were also excluded. Three participants were excluded because of extreme outlying resistin values; the remaining 2902 participants were included in this study. The mean of the total follow up period was 9.1 years, the median of the total follow up period was 11.4 years, and the maximum follow up period was 13.5 years.

2.2 Time to Heart Failure Event

Based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study (39), all first admissions with an overnight stay that was confirmed as related to HF were classified as incident HF. All identified cases were required to have at least one HF diagnosis from a physician and/or a recorded treatment for HF. Survival analysis was used to compare the time until the development of HF event among 2902 subjects.

2.3 Measurement of Exposure

Blood samples were obtained at baseline after overnight fasting, frozen at 70° C and shipped to the central laboratory at the University of Vermont. Serum resistin concentration was measured using a sandwich enzyme-linked immunosorbent assay (ELISA; Linco Research Inc). Intra- and inter-assay coefficients of variation for this assay are 4.5% and 7.4%, respectively.

2.4 Covariate Definitions

Covariates of interest included age, race, gender, body mass index (BMI), smoking status, baseline alcohol consumption, history of clinical diabetes, the presence of left ventricular hypertrophy status, baseline prevalent hypertension status, sitting systolic blood pressure, sitting diastolic blood pressure, imputed abdominal circumference, abdomen visceral fat area, abdomen subcutaneous fat area, heart rate, trunk fat, total fat, baseline serum total cholesterol, baseline serum high density lipoprotein, baseline serum albumin, baseline creatinine and baseline fasting serum glucose.

Race was self-defined by the participants and categorized as white and black. Gender was classified as male and female. Smoking was from self-reported information as current, past, or never. Alcohol consumption was grouped to never, occasional, 1-7 drinks per week, and more than 7 drinks per week. History of clinical diabetes was from self-report of a history of diabetes or use of hypoglycemic medication. Other dichotomous variables included the presence of left ventricular hypertrophy; history of surgical or percutaneous revascularization; electrocardiographic evidence of myocardial infarction; and self-reported history of myocardial infarction or angina accompanied by use of antianginal medications. Hypertension was dichotomized as yes and no, based on self-report of a history of physician diagnosis or use of antihypertensive medication. Physical activity was dichotomized to physically active group (≥ 65.21 kcal per kg per week) and physically inactive group (< 65.21 kcal per kg per week).

BMI, average sitting systolic blood pressure, sitting diastolic blood pressure, abdominal circumference, abdomen visceral fat area, abdomen subcutaneous fat area, heart rate, trunk fat, total fat, one year serum total cholesterol, first year serum high density lipoprotein, first year serum albumin, first year creatinine, and first year fasting serum glucose were retrieved from medical records.

2.5 Statistical Analyses

All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Cary, NC). Demographic and clinical variables were compared between patients who developed HF by the end of study period and patients who did not develop HF. Categorical variables were presented as counts and percentages and compared between

groups with Pearson's chi-square test. Continuous variables were presented as means and standard deviations and compared between groups with the 2-sample *t* test.

The main exposure variable, baseline serum resistin concentration, was categorized into 4 quartiles. The Cochran-Armitage trend test was used to test for a trend in binomial proportions of developing incident HF over 5 years across the quartile groups of baseline serum resistin concentration.

The univariate association between baseline serum resistin and survival until the first HF event was examined by Kaplan Meier's plots overall and in subgroups of males and females, and white and black subjects. Log-rank test was conducted to compare survival curves across baseline serum resistin quartiles.

In order to assess the association between baseline serum resistin concentration and incident HF over 5 years of follow up, interaction and confounding were evaluated before fitting the final model. The continuous baseline serum resistin concentration variable was used in a Cox proportional hazards (PH) model. To assess interaction terms, we began with a Chunk Test by using Cox PH regression with the null hypothesis that all interaction terms equal zero. Based on the Wald Test results, interaction term with highest p-value was dropped from the initial model. After that, a new Chunk Test was reevaluated without the interaction term that was just dropped out of the previous step. This step was repeated for each Chunk test to drop the least significant interaction term. The repetition ended when the remaining interaction terms in the model were all significant ($p<0.05$). By this backward elimination technique, interaction effect was identified.

After performing the interaction assessment, other first order terms besides the exposure variable resistin and terms in the interaction terms were evaluated further for confounding effect. The 10% rule was used in confounding assessment. The gold standard model contained the exposure variable, the interaction term identified, the corresponding first order term for the interaction term, and the remaining 26 covariates. Each of the 26 covariates was removed from the model. If the beta coefficient for the exposure variable resistin changed over 10% after dropping a certain covariate, then this covariate was considered as potential confounder.

We then fit a multivariate Cox PH model to assess the association between baseline serum resistin concentration and incident HF over 5 years while adjusting for potential confounders. Interaction terms and their corresponding first-order term were included if there were any.

PH assumptions for each variable in the final model were assessed by goodness of fit test with Schoenfeld residuals. The 5% significance level was applied to all models.

The study has been approved by the Emory IRB.

3 RESULTS

3.1 Cohort demographics

At baseline a total of 3075 eligible participants were identified from the original cohort. Participants with HF or missing data on HF (n=140) were excluded. Of the 2935 participants without prevalent HF at baseline, 2905 (99.0%) had available serum resistin concentrations. Three participants were excluded because of extreme outlying resistin values; the remaining 2902 participants were included in this study, of which 182 (6.30%) developed HF by the end of study period (Table 1). The mean of the total follow up period was 9.1 years, the median of the total follow up period was 11.4 years, and the maximum follow up period was 13.5 years.

When comparing participants who developed HF by the end of study period to participants who did not develop HF, there were no statistically significant differences in gender and alcohol consumption at baseline; however, there were significant differences according to race, smoking status at baseline, history of clinical diabetes, left ventricular hypertrophy, prevalent hypertension, and prevalent coronary artery disease at baseline. The proportion of black participants who had HF over 5 years of follow up was significantly greater than the proportion of white participants (7.40 vs. 5.50%, p=0.0443). The proportion of current smokers who had HF over 5 years of follow up was significantly greater than the proportion of former smoker and non-smokers (11.6 vs. 6.30 vs. 4.90 %, p<0.0001). Patients with a history of clinical diabetes had a greater proportion of HF than patients without a history of clinical diabetes (9.60 vs. 5.70 %, p=0.0017). Patients with left ventricular hypertrophy at baseline were more likely to have HF during the study period than patients without left ventricular hypertrophy (10.4 vs.

5.70%, p=0.0007). The proportion of patients with prevalent hypertension at baseline who had HF during the study period was significantly higher than the proportion among patients without prevalent hypertension at baseline (8.00 vs. 4.90%, p<0.0001). Patients with prevalent coronary artery disease at baseline had a higher proportion of having HF over 5 years of follow up compared with patient without prevalent coronary artery disease (15.1 vs. 4.60%, p<0.0001).

Mean and standard deviation, together with two-sample t-test result are given for each of the continuous variables to compare participants who developed HF by the end of study period with participants who did not develop HF (Table 2). Age, sitting systolic blood pressure, sitting diastolic blood pressure, heart rate, baseline serum creatinine, baseline serum resistin, and baseline fasting serum glucose were significantly higher for participants who developed incident HF than those who did not; whereas baseline serum albumin and baseline plasma total cholesterol were significantly lower for participants who developed incident HF, compared with those who did not. Other characteristics, including body mass index, physical activity, abdominal circumference, abdomen total area, abdomen visceral fat area, abdomen subcutaneous fat area, trunk fat, total fat, total fat percentage, baseline plasma triglycerides, baseline plasma high density lipoprotein and baseline plasma low density lipoprotein did not vary significantly between the two groups. The mean of age at baseline of patient who had HF during the 5 years follow up period was significantly greater than patients who didn't develop HF (73.9 vs. 73.6, p=0.0498). Patients who had HF during the follow up period had a significant greater sitting systolic blood pressure mean than patient who didn't develop HF (142 vs. 135, p<0.0001). Patients who had HF during the follow up period also had a significant

greater sitting diastolic blood pressure mean than patient who didn't develop HF (72.6 vs.71.3, p=0.0154). The mean of heart rate at baseline of patient who had HF during the 5 years follow up period was significantly greater than patients who didn't develop HF (68.6 vs. 65.2, p<0.0001). Patients with a higher mean of baseline serum creatinine were more likely to have HF than patient with a lower mean of baseline serum creatinine (1.24 vs. 1.05, p<0.0001). Patients who had HF during the follow up period also had a significant greater baseline fasting serum glucose mean than patient who didn't develop HF (116 vs.103, p<0.0001). The mean of baseline serum resistin at baseline of patients who had HF during the 5 years follow up period was significantly greater than patients who did not develop HF (25.1 vs. 19.9, p<0.0001). Patients who had HF during the follow up period also had a significant lower baseline mean plasma total cholesterol levels than patients who did not develop HF (199vs.203, p=0.0408). The mean baseline serum albumin of patients who had HF during the 5 years follow up period was significantly lower than patients who did not develop HF (3.91 vs. 3.98, p=0.0024).

A histogram for serum resistin concentration measured at baseline was plotted to examine its distribution (Figure 1). The distribution was right skewed. Serum resistin concentration was divided into 4 quartiles. The Cochran-Armitage trend test showed an increasing trend of incident HF proportion across the four quartiles of serum resistin concentration measured at baseline ($p < 0.0001$). Compared with concentration of 1.88-14.0 ng/ml of serum resistin, the hazard of getting the first HF among those who having serum resistin concentration of 14.0-18.1 ng/ml was 1.37 (95%CI: 0.87-2.16)，the hazard of getting the first HF among those who having serum resistin concentration of 18.1-24.3 ng/ml is 1.85 (95%CI: 1.20-2.85), and the hazard of developing the first HF

among those who having serum resistin concentration of 24.3-221 ng/ml is 3.44 (95%CI: 2.31-5.11)(Table 3.1). It suggested that participants who had high resistin concentration were more likely to have incident HF over 5 years of follow up. Chi-square p-value showed the serum resistin concentration differed between the white and black ($p<0.0001$), same as for the difference between males and females ($p= 0.0333$).

3.2 Kaplan-Meier estimate curves for incident HF

Survival curves were plotted by serum resistin quartiles and further stratified by gender and race respectively over 5 years of duration (Figure 2, 3). Survival curves were significantly different among resistin quartile groups (log-rank test p-values <0.0001). The lowest quartile of serum resistin had the highest survival probability, followed by 2^{nd}, 3^{rd} quartiles, and lastly the 4^{th} quartile.

3.3 Association of resistin with incident HF over 5 years of follow up

Serum resistin concentration was associated with incident HF during the follow-up period [raw HR per 10 ng/ml increase = 1.21 (95% CI: 1.16-1.27), p=0.005]. The multivariable adjusted effect of resistin HR per 10-ng/ml increase in the overall population is 1.13 (95% CI: 1.11-1.15, p=0.14).

By Wald test and backward elimination technique, only dichotomous variable physical activity status was found to have interaction with the effect of resistin on the incident HF during the 5 year of follow up. For physically active participants (≥ 65.2 kcal per kg per week), the hazard of incident HF is 1.03 (95% CI: 1.00-1.07) fold higher per one ng/ml increase in serum resistin level (Table 4). For physically inactive participants (<65.2 kcal per kg per week), the hazard of incident HF is 1.02 (95% CI:

1.01-1.03) fold higher per one ng/ml increase in serum resistin level (Table 5). Equally the hazard of incident HF was 1.21 (95% CI: 1.19-1.23) and 1.22 (95% CI: 1.21-1.24) per 10 ng/ml increase in serum resistin level for participants with physical activity and physical inactivity respectively. The effect of serum resistin level on the incident HF was slightly higher for physically active participants compared with that in physically inactive participants.

By 10% rule, five variables including sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and baseline serum albumin concentration were found to confound the effect of resistin on the incident HF during the 5 year of follow up.

3. 4 Evaluation of PH assumption

To evaluate PH assumption, goodness of fit test was conducted by using Schoenfeld residuals. Correlation test between the Schoenfeld residuals and ranked failure time was conducted. The corresponding p-values were shown (Table 6). The p-values for resistin, average sitting systolic blood pressure, heart rate, trunk fat, total fat percentage, and serum albumin concentration, physical activity and interaction term between resistin and physical activity were all ≥ 0.05. We failed to reject the null hypothesis, suggesting that the PH assumption was reasonable.

4. DISCUSSION

Our study analysis was based on a total of 2902 participants who were HF free at baseline and did not have missing or extreme baseline serum resistin concentration. With the aim of evaluating the association between serum resistin level and incident HF over 5 years of follow up, we first performed primary analysis on baseline serum resistin concentration. The continuous variable baseline resistin concentration was first categorized into quartiles. The Cochran-Armitage trend test was performed to confirm a significant increasing trend of risk of incident HF across the four quartiles of resistin level. This was consistent with the previous studies (9). Kaplan-Meier survival curves were plotted for incident HF by serum resistin quartiles. The log-rank test suggested incident HF differed significantly across the resistin quartiles overall as well as in gender and race subgroups.

We then screened all the variables available in the dataset to identify interaction and confounding effect for resistin. We first assessed whether or not any covariate had interaction effect with resistin by using Wald test and backward elimination technique. The result showed only physical activity status had an interaction with the effect of serum resistion on the incident HF over 5 years of follow up. The rest covariates were later assessed whether or not they were an effect confounder by using 10% rule. After identification of interaction terms and confounders, multivariate Cox PH was fit with the main exposure variable resistin, the interaction terms and confounders.

As a result we developed a Cox PH model showing the increased incident HF was highly associated with higher serum resistin concentration after adjustment for sitting systolic blood pressure, heart rate, trunk fat, total percentage of fat and the baseline serum

albumin. The effect of serum resistin on incident HF over 5 years was modified by physical activity. The effect of serum resistin level on the incident HF was slightly higher for physically active participants compared with that in physically inactive participants.

These findings were consistent with previous findings (9, 38). Although previous studies had identified several individual risk factors with incident HF, no comprehensive and internal validated risk prediction models of incident HF with resistin had been established. The Framingham Heart Study had developed a model in a community-based cohort with known hypertension, coronary heart disease (CHD) and valvular heart disease (VHD), which were known high risk factors of HF (31). This kind of participants accounted for about a half of Health ABC study population. It not only adds to current studies on incident HF on elder people, but also particularly gives more interesting evidence about the importance of studying resistin as a novel metabolic marker considered its association with obesity, metabolic syndrome and diabetes (39).

However, limitations did exist in this study. Diagnosis of HF was depending on overnight stay in hospital but not a comprehensive analysis of symptoms, signs, chest radiograph results or echocardiography. This may cause the risk of HF to have been underestimated due to non-hospitalized HF. Besides, because the definition of HF was ambiguous and complicated, it was likely for misclassification that may occurred of incident HF over the follow up period. The other shortcoming was that the Health ABC study didn’t collect echocardiography data at baseline, which might have caused the inclusion of some participants with subclinical heart disease.

In addition, collinearity was not tested between each explanatory variable. For future work, it might be good to test collinearity before the final multivariate modeling. Also, the use of cox PH model was built on several assumptions. Failure to meet these assumptions such as incorrect link function, non-constant coefficient, hazard ratios, and incorrect systematic component might make the results questionable. We only conducted goodness of fit test based on Schoenfeld residuals. More assumption test might be needed to make our results more reliable.

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TABLES AND FIGURES

Table 1 Comparison of sociodemographic, clinical, and program characteristics (discrete variables) by incident HF over 5 years of follow up (N=2,902) - Health, Aging, and Body Composition (Health ABC), 1997-1998

Variable	Total	Col %	Having incident HF over 5 years		Median Survival	Chi-square
			Freq	Row%	(days)	p-value*
Race						
White	1705	58.8%	94	5.50%	1063	0.0443
Black	1197	41.2%	88	7.40%	746	
Gender						
Male	1394	48.0%	95	6.80%	834	0.2457
Female	1508	52.0%	87	5.80%	985	
Smoking status at baseline						
Never	1284	44.3%	63	4.90%	962	<.0001
Former smoker	1311	45.2%	83	6.30%	818	
Current smoker	303	10.5%	35	11.6%	958	
Alcohol consumption at baseline						
Never	1441	49.8%	92	6.40%	956	0.7239
Occasional	613	21.2%	40	6.50%	790	
1-7 drinks/week	623	21.5%	34	5.50%	1066	
> 7 drinks/week	214	7.40%	16	7.50%	883	
History of clinical diabetes						
No	2474	85.3%	140	5.70%	986	0.0017
Yes	425	14.7%	41	9.60%	683	
Left ventricular hypertrophy						
No	2557	88.1%	146	5.70%	981	0.0007

	Yes	345	11.9%	36	10.4%	774	
Prevalent hypertension at baseline							
	No	1647	56.8%	81	4.90%	1048	<.0001
	Yes	1255	43.2%	101	8.00%	834	
Prevalent coronary artery disease at baseline							
	No	2431	83.8%	111	4.60%	958	<.0001
	Yes	471	16.2%	71	15.1%	944	
Total		2902	100%	182	6.30%	949	

*Chi-square was based on risk of HF by race, gender, smoking status at baseline, alcohol consumption at baseline, history of clinical diabetes, left ventricular hypertrophy, prevalent hypertension at baseline and prevalent coronary artery disease at baseline.

Table 2 Comparison of sociodemographic, clinical, and program characteristics (continuous variables) by incident HF over 5 years of follow up (N=2,902) - Health, Aging, and Body Composition (Health ABC), 1997-1998

Variable	N	Not having incident HF over 5 years		Having incident HF over 5 years		2-sample t-test p-value
		Mean	±SD	Mean	±SD	
Age at year baseline clinic visit	2833	73.6	±2.86	73.9	±2.98	0.0498
Body mass index, kg/m^2	2833	27.3	±4.81	28.0	±4.91	0.0973
Sitting systolic BP, mm hg	2833	135	±20.5	142	±25.4	<.0001
Sitting diastolic BP, mm hg	2833	71.3	±11.6	72.6	±13.0	0.0154
Physical activity (kcal/kg/week)	2833	83.3	±68.8	79.1	±74.9	0.8261
Abdominal circumference(cm)	2830	99.4	±13.3	101	±12.2	0.0999
Abdomen total area (cm-sq)	2647	684	±165	698	±159	0.5354
Abdomen visceral fat area (cm-sq)	2728	142	±67.1	149	±67.2	0.2271
Abdomen subcutaneous fat area (cm-sq)	2647	285	±121	282	±127	0.4554
Heart rate	2832	65.2	±11.0	68.6	±12.4	<.0001
Trunk fat (gm)	2783	13425	±4890	13745	±4737	0.4147
Total fat (gm)	2813	26748	±8753	26974	±8853	0.7353
Total %fat	2730	35.0	±7.80	34.4	±7.99	0.2488
Baseline plasma total cholesterol (mg/dl)	2804	203.2	±38.3	199	±41.7	0.0408
Baseline plasma triglycerides (mg/dl)	2804	137.5	±78.3	149	±121	0.7654
Baseline plasma high density lipoprotein (mg/dl)	2802	54.3	±17.0	51.8	±17.4	0.1315
Baseline plasma low density lipoprotein (mg/dl)	2766	122	±34.6	117	±35.0	0.1433

Baseline serum albumin (g/dl)	2809	3.98	±0.31	3.91	±0.34	0.0024
Baseline serum creatinine (mg/dl)	2809	1.05	±0.38	1.24	±0.67	<.0001
Baseline serum resistin (ng/ml)	2807	19.9	±10.7	25.1	±16.1	<.0001
Baseline fasting serum glucose (mg/dl, .t if not fasting)	2745	103	±31.6	116	±49.8	<.0001

Table 3 Bivariate analysis for quartiles of serum resistin concentration - Health, Aging, and Body Composition (Health ABC), 1997-1998

1) Serum resistin concentration by incident HF over 5 years of follow up

Serum Resistin Concentration Quartile		Incident HF over 5 years						Cochran-Armitage Trend test p-value
		Case	Total	Risk (%)	Hazard Ratio	95% CI	PT[a]	
1	1.88~14.0 ng/ml	27	735	3.70	1.00		3620	<0.0001[b]
2	14.0~18.1 ng/ml	36	737	4.90	1.35	(0.87, 2.16)	3689	
3	18.1~24.3 ng/ml	47	725	6.50	1.82	(1.20, 2.85)	3690	
4	24.3~221 ng/ml	72	705	10.2	3.98	(2.31, 5.11)	3647	
Total		182	2902	6.30				

a. PT = Person time (days) of incident HF during 5 years of follow up
b. Cochran-Armitage trend test showed the existence of a significant increasing trend of incident HF risk across four quartiles of serum resistin concentration.

2) Serum resistin concentration by race

Resistin Concentration Quartile		Race							
		White				Black			
		Case	Total	Risk (%)	Chi-square p-value	Case	Total	Risk (%)	Chi-square p-value
1	1.88~14.0 ng/ml	12	405	2.96	0.004*	15	330	4.55	0.002*
2	14.0~18.1 ng/ml	24	469	5.12		12	268	4.48	
3	18.1~24.3 ng/ml	28	504	5.56		19	221	8.60	
4	24.3~221 ng/ml	30	327	9.17		42	378	11.1	
Total		94	1705	5.51		88	1197	7.35	

* Chi-square p-value showed the risk of incident HF across serum resistin concentration quartiles were significantly different for either of the race subgroups (white/black).

3) Serum resistin concentration by gender

		Gender							
		Male				Female			
	Serum Resistin Concentration Quartile	Case	Total	Risk (%)	Chi-square p-value	Case	Total	Risk (%)	Chi-square p-value
1	1.88~14.0 ng/ml	16	321	4.98	0.027*	11	414	2.66	<.0001*
2	14.0~18.1 ng/ml	18	355	5.07		18	382	4.71	
3	18.1~24.3 ng/ml	26	370	7.03		21	355	5.92	
4	24.3~221 ng/ml	35	348	10.00		37	357	10.3	
	Total	95	1394	6.81		87	1508	5.77	

* Chi-square p-value showed the risks of incident HF across serum resistin concentration quartiles were significantly different for either of the gender subgroups (male/female).

Table 4 Multivariate Cox PH model to test association between resistin and incident HF over 5 years of follow up for patient with high physical activity- Health, Aging, and Body Composition (Health ABC), 1997-1998

Analysis of Maximum Likelihood Estimates							
Parameter	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**P**	**Hazard Ratio**	**95% CI***	
Baseline serum resistin (per 10 ng/ml)	0.190	0.071	7.675	0.006	1.209	1.192	1.226
Baseline serum resistin (per ng/ml)	0.019	0.007	7.675	0.006	1.019	1.006	1.033
Sitting systolic BP (mm hg)	0.021	0.003	40.618	<.0001	1.021	1.015	1.028
Heart rate	0.033	0.006	28.387	<.0001	1.033	1.021	1.046
Trunk fat (100gm)	0.002	0.002	0.799	0.371	1.003	0.997	1.009
Total %fat	-0.030	0.013	5.066	0.024	0.971	0.946	0.996
Baseline serum albumin (g/dl)	-0.927	0.246	14.174	0.0002	0.396	0.244	0.641
Physical Activity(kcal/kg/week)	-0.401	0.309	1.684	0.195	0.67	0.365	1.227
Resistin*Physical Activity	0.015	0.011	1.711	0.191	1.015	0.993	1.037

*CI = confidence interval

Note: For physically active participants (≥ 65.21 kcal per kg per week), the hazard of incident HF is exp(0.019+0.015) = 1.035 fold higher per one ng/ml increase in serum resistin level, with 95% CI equals to 1.035±1.96*(0.007+0.011) = (95% CI: 1.000-1.070)

Table 5 Multivariate Cox PH model to test association between resistin and incident HF over 5 years of follow up for patient with low physical activity- Health, Aging, and Body Composition (Health ABC), 1997-1998

Analysis of Maximum Likelihood Estimates							
Parameter	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**P**	**Hazard Ratio**	**95% CI***	
Baseline serum resistin (per 10 ng/ml)	0.200	0.072	8.362	0.004	1.221	1.205	1.238
Baseline serum resistin (ng/ml)	0.020	0.007	8.362	0.004	1.020	1.006	1.034
Sitting systolic BP (mm hg)	0.021	0.004	22.658	<.0001	1.021	1.013	1.030
Heart rate	0.024	0.008	8.231	0.004	1.025	1.008	1.042
Trunk fat (100gm)	0.002	0.003	0.066	0.797	1.001	0.995	1.006
Total %fat	-0.016	0.01817	0.751	0.386	0.984	0.950	1.020
Baseline serum albumin (g/dl)	-0.480	0.33569	2.044	0.153	0.619	0.320	1.195

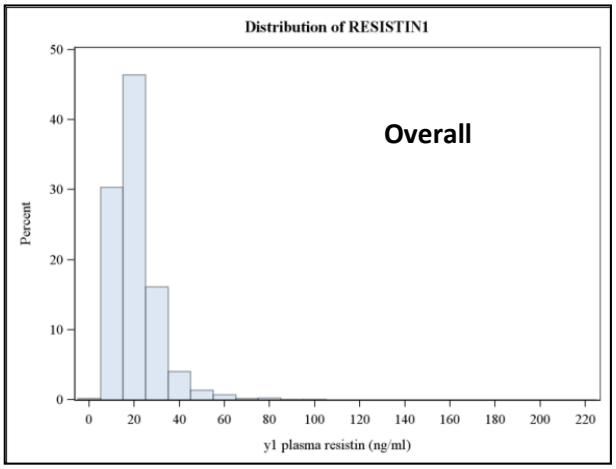
*CI=confidence interval

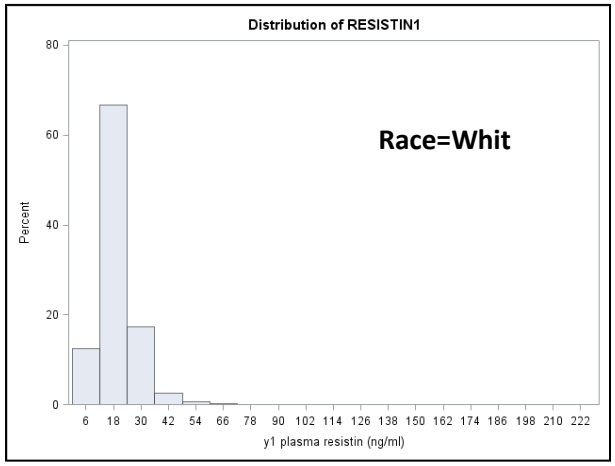
Note: For physically inactive participants (≥ 65.21 kcal per kg per week, where physical activity equals to 0), the hazard of incident HF is exp(0.020)=1.020 fold higher per one ng/ml increase in serum resistin level, with 95% CI equals to (95% CI: 1.006-1.034)

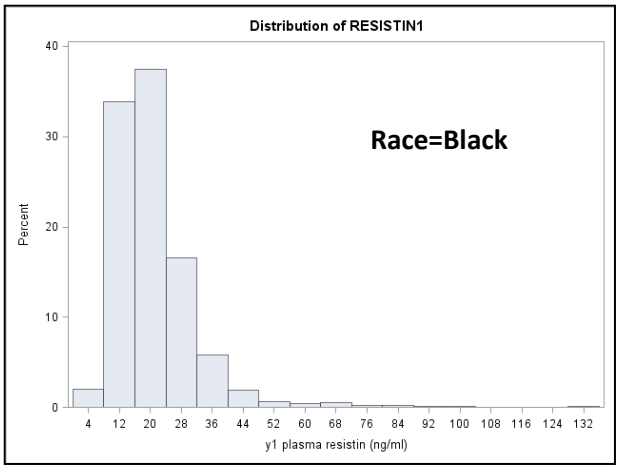
Table 1 Goodness of Fit Test - Pearson correlation test between the Schoenfeld residuals and ranked failure time - Health, Aging, and Body Composition (Health ABC), 1997-1998

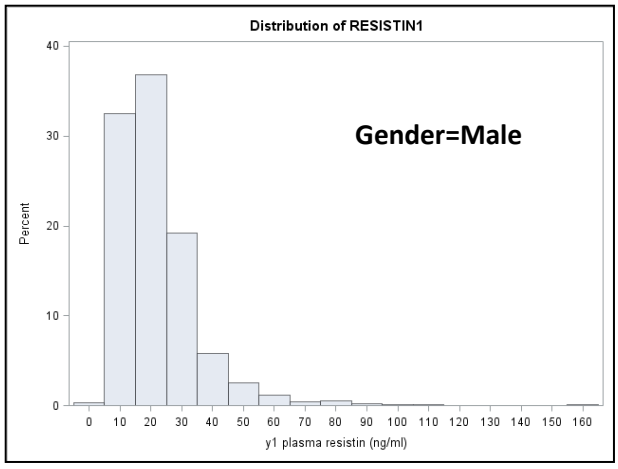
	Pearson Correlation Coefficients Prob > |r| under H0: Rho=0							
	Baseline serum resistin	**Sitting systolic BP**	**Heart rate**	**Trunk fat**	**Total %fat**	**Baseline serum albumin**	**Physical Activity**	**Resistin*Physical Activity**
TIMERANK[a]	0.042	0.082	0.018	-0.090	-0.003	0.108	0.150	0.130
p-value[b]	0.582	0.283	0.811	0.240	0.972	0.157	0.048	0.088

a. Ranked Failure Time was a variable that ranks the order of failures. The subject who had the first (earliest) event got a value of 1, the next got a value of 2, and so on.
b. P-value > 0.05 suggested of zero correlation, and thus the PH assumption was reasonable.









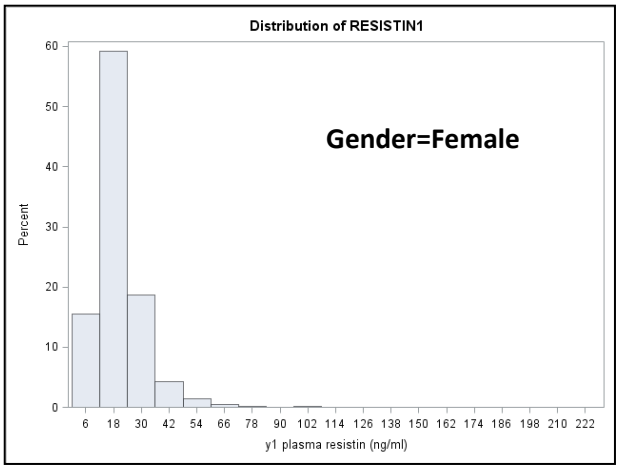


Figure 1 Distribution of baseline serum resistin concentration overall and in subgroups of white/black, male/female. They were all right skewed - Health, Aging, and Body Composition (Health ABC), 1997-1998

Overall Incident HF by Serum Resistin Quartiles, Log-Rank Test p-value <0.0001

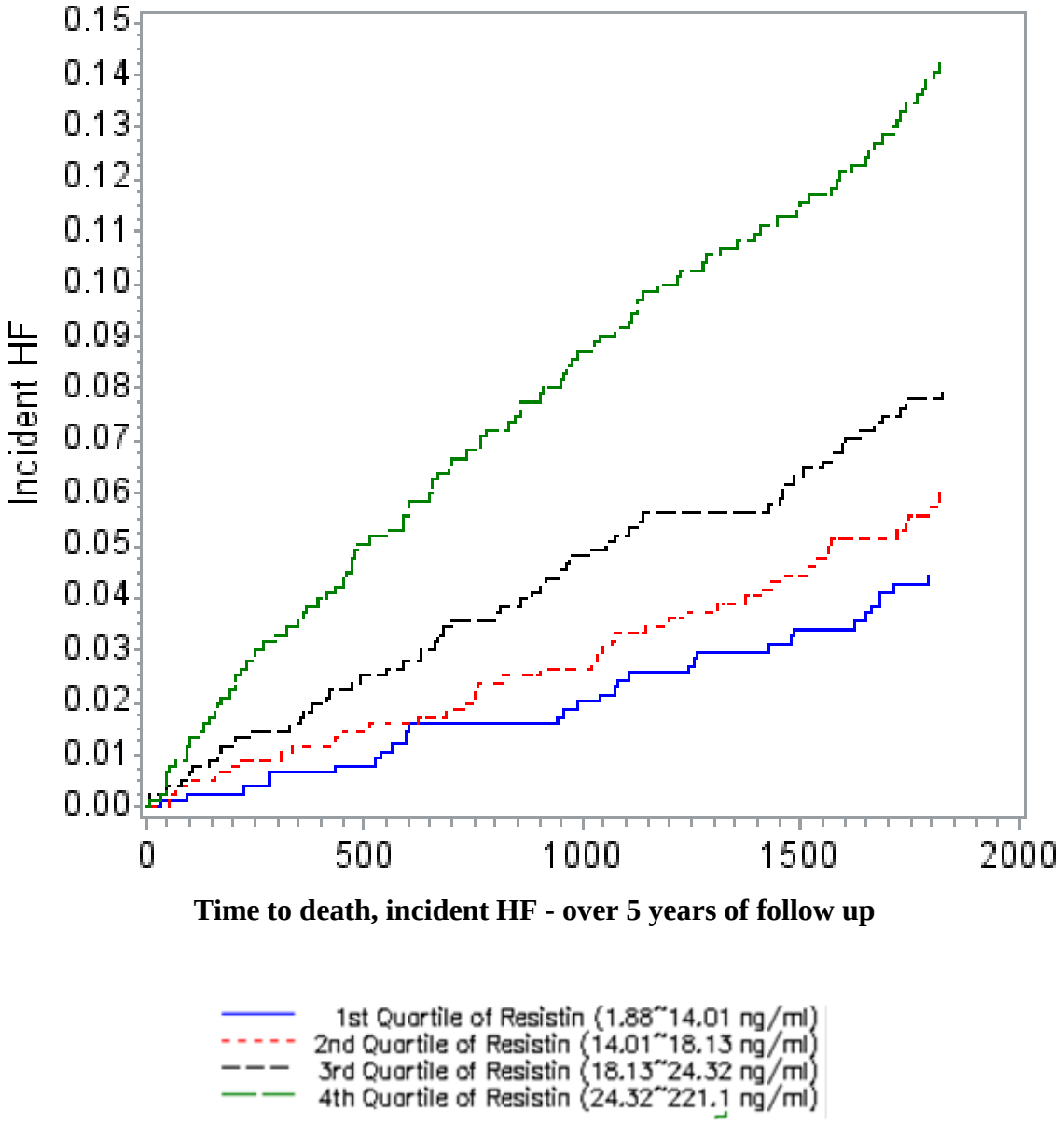


Figure 2 Overall incident HF by serum resistin quartiles, The log-rank test p-value (< .0001) suggested the incident HF changes significantly across the resistin quartiles - Health, Aging, and Body Composition (Health ABC), 1997-1998

Incident HF by Serum Resistin Quartiles in Subgroups

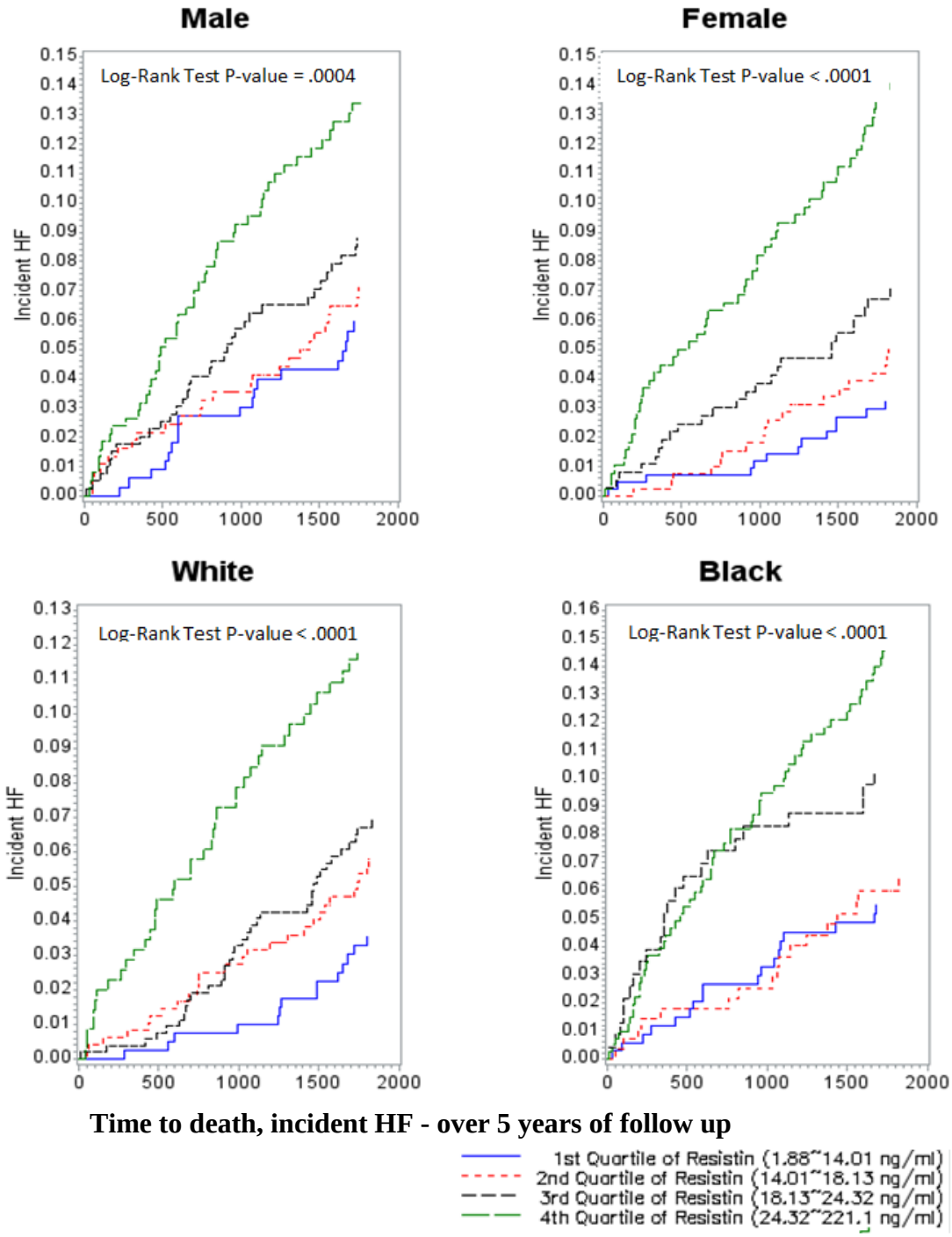


Figure 3 Incident HF by serum resistin quartiles in subgroups. The log-rank test p-value (either 0004 or < .0001) suggested the incident HF changed significantly across the resistin quartiles in subgroups of male, female, the white, and the black - Health, Aging, and Body Composition (Health ABC), 1997-1998