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Inflammation as a Mediator of the Association Between Race and Atrial Fibrillation: Results from the Health, Aging, and Body Composition Study

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Abstract

Background—Despite a lower prevalence of established atrial fibrillation (AF) risk factors, Whites exhibit substantially higher rates of this arrhythmia compared to Blacks. The mechanism underlying this observation is not known. Both inflammation and obesity are risk factors for AF, and adipose tissue is a known contributor to systemic inflammation.

Objectives—We sought to determine the degree to which racial differences in AF risk are explained by differences in inflammation and adiposity.

Methods—Baseline serum inflammatory biomarker concentrations and abdominal adiposity (assessed by computed tomography) were quantified in a subset of Black and White participants without prevalent AF in the Health, Aging, and Body Composition (Health ABC) Study. Participants were prospectively followed for the diagnosis of AF using study ECGs and Medicare

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claims data. Cox proportional hazards models were used to determine the adjusted relative hazard of incident AF between races before and after biomarker adjustment.

Results—Among 2,768 participants (43% Black), 721 developed incident AF over a median follow up of 10.9 years. White race was associated with a heightened adjusted risk of incident AF (HR 1.55, 95% CI 1.30 to 1.84, $p < 0.001$). Abdominal adiposity was not associated with AF when added to the adjusted model. Among the studied biomarkers, adiponectin, TNF-α, TNF-α SR I, and TNF-α SR II concentrations were each higher among Whites and independently associated with a greater risk of incident AF. Together, these inflammatory cytokines mediated 42% (95% CI 15 to 119%, $p = 0.004$) of the adjusted race-AF association.

Conclusions—Systemic inflammatory pathways significantly mediate the heightened risk of AF among Whites. The higher level of systemic inflammation and concomitant increased AF risk in Whites is not explained by racial differences in abdominal adiposity or the presence of other pro-inflammatory cardiovascular comorbidities.

Keywords

atrial fibrillation; race; inflammation

Introduction

Despite a lower prevalence of traditional atrial fibrillation (AF) risk factors, Whites exhibit substantially higher rates of this arrhythmia compared to Blacks (1, 2). A better understanding of the intermediary factors responsible for this association could yield important insight into the pathogenesis of the most commonly encountered cardiac arrhythmia.

Inflammation and its downstream effects, including atrial fibrosis, are thought to play a central role in AF development and perpetuation (3, 4). Systemic inflammation can be quantified through measurement of serum inflammatory cytokine levels, and previous investigations have associated concentrations of C-reactive protein (CRP) (5–7) and interleukin (IL)-6 (8) with clinical AF risk. Many of these inflammatory markers are secreted or regulated by adipose tissue (9), and a growing body of literature has linked obesity with heightened AF susceptibility (10–12). Notably, racial differences in both inflammation and adiposity have also been reported (13–16). Furthermore, Whites tend to have greater visceral abdominal adiposity compared to Blacks (17), providing a potential mechanistic explanation for differences in inflammation by race.

In light of the above associations, we hypothesized that racial differences in inflammation, secondary to racial variation in abdominal adiposity, explain the substantially divergent risk of AF between Whites and Blacks. The Health, Aging, and Body Composition (Health ABC) Study was therefore utilized to determine the degree to which inflammatory cytokines and adiposity mediate the association between race and AF.

Methods

Health, Aging, and Body Composition Study Design

Health ABC is a population-based cohort study sponsored by the National Institute on Aging. Eligibility, enrollment, and follow-up protocols have been previously published (18). In brief, 3,075 White or Black individuals 70 to 79 years of age were recruited between 1997 and 1998 from a random sample of Medicare beneficiaries residing in two urban areas (Pittsburgh, Pennsylvania and Memphis, Tennessee). After undergoing a baseline medical history, physical exam, laboratory assessment, and electrocardiogram (ECG), participants were followed with yearly clinic visits and interim telephone contact every six months. All participants provided written, informed consent upon study enrollment.

Study Cohort

From the overall Health ABC cohort, individuals with prevalent AF were excluded. Participants actively receiving chemotherapy or taking oral steroids were also excluded, as we reasoned that the inflammatory conditions underlying or induced by such treatments could confound the association between race and inflammatory markers. Individual inflammatory cytokine and abdominal adiposity analyses were restricted to participants with available baseline biomarker measurements.

Inflammatory Marker Measurement

At the baseline study visit, participants underwent morning venipuncture after an overnight fast. Serum samples were frozen at −70° C and stored in a core laboratory at the University of Vermont (Burlington, Vermont). A total of 9 inflammatory markers were measured as part of the Health ABC protocol. Because the relative importance of these candidate inflammatory cytokines in AF risk prediction has not been well established, we considered all biomarkers in our initial analysis. Adiponectin, interleukin-6, TNF-α, CRP, and plasminogen activator inhibitor (PAI)-1 quantification was attempted on all participants, while soluble receptor concentrations (IL-2 SR, IL-6 SR, TNF-α SR I, and TNF-α SR II) were measured on a sub-sample of 1,367 individuals. IL-6, TNF-α, IL-2 SR, IL-6 SR, TNF-α SR I, and TNF-α SR II were measured in duplicate using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, Minnesota). CRP levels were also measured in duplicate by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, California). PAI-1 was measured from citrated plasma using a two-site ELISA (Center of Molecular and Vascular Biology, University of Leuven, Belgium), while adiponectin was measured in duplicate by radioimmunoassay (Linco Research, St. Charles, Missouri). Assay detectable limits and performance characteristics have been previously described (19).

Abdominal Adiposity Measurements

Abdominal subcutaneous and visceral adiposity were quantified for each participant using computed tomographic (CT) images obtained in the axial plane at the level of L4-L5 with a 120 kilovolt tube voltage, 200–250 milliampere tube current, and 10 millimeter slice thickness (20). Participants enrolled at the Memphis site were imaged with a Somatom Plus

4 (Siemens, Erlangen, Germany) or a Picker PQ 2000S scanner (Marconi Medical Systems, Cleveland, Ohio), while the Pittsburgh center used a 9800 Advantage scanner (General Electric, Milwaukee, Wisconsin). Images were analyzed in a core laboratory. The fascial plane of the internal abdominal wall was manually identified on each CT image and used to distinguish visceral from subcutaneous fat. Adiposity area was quantified by multiplying the adipose soft tissue pixel count by pixel area (Interactive Data Language Software, ITT Visualization Solutions, Boulder, Colorado).

Covariate Assessment

Race, prevalent health conditions, medication usage, tobacco history, and alcohol consumption were self-reported by participants at baseline using an interview-administered standardized questionnaire. Alcohol use was dichotomized as < or ≥ 1 drink per week. Diabetes was present if the participant reported a history of diabetes or was taking an antihyperglycemic medication. Coronary artery disease was defined as a history of angina, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery. Height was assessed barefoot with a wall-mounted stadiometer to the nearest 0.1 centimeter. Weight was quantified using a balance beam scale to the nearest 0.1 kilogram. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Blood pressure was obtained in a seated position and determined by averaging two successive measurements. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or a participant reported history of hypertension with concomitant antihypertensive use.

Atrial Fibrillation Ascertainment

Participants were linked to Centers for Medicare Services databases and AF was identified using the International Classification of Diseases, Ninth Edition (ICD-9) code 427.31 recorded during an inpatient hospitalization or ambulatory healthcare encounter. Prevalent AF was present if pre-enrollment Medicare claims data revealed AF ICD-9 coding (between 1992 and study enrollment) or if the baseline study ECG demonstrated AF. Incident AF was determined using Medicare claims ICD-9 data or the study year 4 ECG. ECGs were analyzed using the Minnesota Coding system and visually inspected for accuracy in a core laboratory at St. Louis University Medical Center (St. Louis, Missouri).

Statistics

Continuous variables with a normal distribution are presented as mean ± standard deviation (SD) and were compared using t-tests. Non-normally distributed continuous variables are presented as medians with interquartile ranges (IQR) and were compared using Kruskal-Wallis tests. The association between categorical variables was determined using Chi-squared tests. For interpretability and to ensure log-linearity, we used log base 2 transformations of serum cytokine concentrations. Successful normalization of the log-transformed variables was subjectively assessed by comparing histogram and Q-Q plots before and after transformation. Cox proportional hazards models were used to determine the association between race and AF both before and after controlling for confounders identified *a priori*. Participant enrollment site (Memphis versus Pittsburgh) was included in

all adjusted models. Hazard ratios for the association between cytokines and AF can be interpreted as the increased hazard for each doubling in cytokine concentration.

The extent to which inflammation mediates the race-AF association was first assessed using an average causal mediation effect methodology (21). Briefly, adjusted pooled logistic regression with annual time periods was used to calculate the percentage of total effect mediated by each inflammatory cytokine. To estimate the overall inflammatory mediation effect, all serum markers that significantly mediated the race-AF association in the above models ($p < 0.05$) were added to a single adjusted model and the percent treatment effect methodology (22) was used to facilitate the inclusion of multiple mediators. Confidence intervals for mediation statistics were obtained using bootstrap resampling with 1,000 repetitions.

Data were analyzed using Stata 12 (StataCorp, College Station, Texas, USA). A two-tailed $p < 0.05$ was considered statistically significant. All participants provided written informed consent upon enrollment. Certification to use deidentified Health ABC data was obtained from the University of California, San Francisco Committee on Human Research.

Results

Among the 3,075 Health ABC participants, individuals with prevalent AF (n = 211), receiving chemotherapy (n = 35), or treated with oral steroids (n = 61) were excluded. The remaining cohort was comprised of 1,179 (43%) Black and 1,589 (57%) White adults. Black participants were more likely to be female, less frequently consumed alcohol, had a greater mean BMI, and had a higher prevalence of medical comorbidities including hypertension and diabetes (Table 1).

Race and Atrial Fibrillation

Over a median 10.9 years of follow up, 721 participants were diagnosed with incident AF. In bivariate analyses, Whites demonstrated a significantly increased risk of incident AF compared to Blacks (Table 2). After controlling for the known AF risk factors in Table 2, White race remained associated with a 55% increase in AF risk (HR 1.55, 95% CI 1.30 to 1.84, $p < 0.001$). Nearly all *a priori* risk factors were associated with AF in both bivariate and multivariate models (Table 2). Notably, the association between diabetes and AF was of borderline statistical significance in both models, BMI was not significantly associated with increased AF risk, and statin therapy did not appear to have a definitive protective effect. Study site was not associated with incident AF in either bivariate or multivariate models.

Race, Inflammatory Cytokines, and Atrial Fibrillation

White participants demonstrated significantly elevated serum levels of adiponectin, IL-6 SR, IL-2 SR, TNF-α, TNF-α SR I, and TNF-α SR II compared to Blacks (Figure 1). Higher inflammatory cytokine concentrations were associated with increased AF risk after controlling for established AF risk factors, although this association was of borderline significance for IL-2 SR and did not meet statistical significance for IL-6 SR and PAI-1 (Table 3).

To be considered a potential mediator of the race-AF association, a candidate cytokine was required to have a significantly higher concentration among Whites and a significant association with AF after adjustment for race and other risk factors. Adiponectin, TNF-α, TNF-α SR I, and TNF-α SR II each met these criteria. When these biomarkers were individually added to a multivariate model containing the known AF risk factors in Table 2, significant mediation of the race-AF association was observed for each biomarker (Figure 2). When these four cytokines were simultaneously included in the same multivariate race-AF model, the proportion of the race-AF association mediated (i.e. the proportion of the race-AF relationship explained by racial differences in cytokine concentration) was 42.2% (95% CI 15.2 to 118.9%, p = 0.004).

Race, Adiposity, and Atrial Fibrillation

Among the 2,768 participants included in incident AF analyses, 2,664 (96%) and 2,581 (93%) had adequate visceral and subcutaneous CT adiposity measurements, respectively. Whites demonstrated a significantly higher mean abdominal visceral adiposity area compared to Blacks (153 ± 70 versus 130 ± 62 cm^2, p < 0.001), while Blacks had a significantly higher mean subcutaneous fat area (314 ± 139 versus 267 ± 103 cm^2, p < 0.001). In bivariate analyses, each 10 cm^2 increase in visceral abdominal fat area was associated with a 2% increased risk of incident AF (HR 1.02, 95% CI 1.01 to 1.03, p < 0.001). Subcutaneous fat area, on the other hand, was not significantly associated with incident AF (HR 0.99 for each 10 cm^2 increase in area, 95% 0.99 to 1.00, p = 0.078). In multivariate models adjusting for the known AF risk factors listed in Table 2, neither visceral nor subcutaneous abdominal fat area was significantly associated with AF. Because adiposity measurements were not independently associated with AF risk, further mediation analyses incorporating these variables were not performed.

Discussion

In a large, well-characterized, population-based sample of older Black and White adults, race was associated with significant differences in AF risk, abdominal adiposity, and serum inflammatory marker concentration. Although abdominal adiposity was not associated with incident AF after controlling for other established risk factors, adiponectin, TNF-α, TNF-α SR I, and TNF-α SR II concentrations were each higher among Whites and associated with a greater adjusted risk of incident AF. The attenuation of the race-AF association after controlling for these cytokines indicates that approximately 40% of the elevated risk of AF among Whites may be attributed to racial differences in inflammation.

The relation between serum inflammatory cytokines and AF risk has been previously described in multiple settings. Both CRP (5–7) and IL-6 (8) are independently associated with AF, even after adjustment for established AF risk factors. Although a significant relationship between adiponectin and AF was not observed in the Framingham Offspring Study (23), a more recent investigation from the Busselton Health Study did identify a significant association (24). The association between TNF-α and AF has only previously been described using a case-control study design (25), and our current investigation represents the first description of the association between this biomarker and incident AF

using a community-based cohort. Because these inflammatory biomarkers were measured at baseline in a cohort of individuals without known AF, these findings strongly support the hypothesis that systemic inflammation contributes to the clinical arrhythmogenesis.

Although we hypothesized that racial differences in abdominal adiposity could account for racial differences in AF risk via inflammatory cytokine production, we did not observe a significant adjusted association between CT-derived adiposity measurements and AF. This suggests that mechanisms distinct from abdominal fat cytokine production, such as genetic differences or environmental exposures, explain the difference in serum biomarker concentrations by race. It also remains possible that CT measurements of abdominal visceral and subcutaneous adiposity do not sufficiently quantify the fat stores responsible for generating the inflammatory cytokines important for AF pathogenesis; recent data suggests pericardial fat is associated with AF (26) and may contribute to an inflammatory response (27). It is also notable that we did not observe an association between BMI and AF. Although BMI has been independently associated with AF in the Framingham (10) and Atherosclerosis Risk in Communities (ARIC) (12) cohorts, BMI did not predict AF in the Cardiovascular Health Study (CHS) (28). The absence of an association in our Health ABC cohort could be explained by cohort characteristics (CHS and Health ABC, for instance, enrolled older participants compared to Framingham and ARIC), by differences in comorbidity characterization, or because BMI is an imperfect surrogate for more important pathologic mediators of AF risk, such as accumulation of pericardial fat.

Recent evidence derived from multiple racial and ethnic groups suggests the association between race and AF is due to heightened AF risk among Whites rather than a protective effect unique to Blacks (1). Consistent with this observation, increasing European ancestry among African Americans is an independent risk factor for AF (28). The underlying mechanism through which White race and European ancestry increase AF risk is unknown. Serum concentrations of tumor necrosis factor (TNF)-α (13), IL-6 (13), CRP (14), and adiponectin (15) are known to differ by race, and greater European ancestry among African Americans predicts higher levels of adiponectin, CRP, IL-2 soluble receptor (SR), IL-6 SR, and TNF-α SR II (16). The substantial proportion of the race-AF association mediated by inflammation adds to the understanding of AF pathogenesis and could have important treatment implications. The association between serum inflammatory marker concentration and incident AF persisted after adjustment for other exposures and cardiovascular conditions known to be linked with increased systemic inflammation, including coronary artery disease and heart failure. Although speculative, this finding could suggest that the inflammatory pathways important for AF pathogenesis are distinct from those associated with these other comorbid conditions. Furthermore, our mediation findings indicate that inflammation is a more prominent and, as a result, more important driver of AF risk among Whites.

From a clinical standpoint, these results suggest that interventions targeting inflammation specific to AF pathogenesis may be especially important for AF risk reduction and that the efficacy of such therapies may differ by race. Indeed, inflammation-related AF may be a specific disease subtype amenable to tailored therapies. It has recently been shown that randomization to a weight loss intervention results in both a reduction in serum CRP

concentration and in AF symptom burden and severity (29). Whether more targeted anti-inflammatory treatments could further improve AF outcomes remains untested.

Potential limitations of this analysis should be recognized. Race was self-reported by study participants. Importantly, nearly all investigations examining the association between race and AF have used this methodology. In addition, inaccurate self-reporting of race would likely bias our results towards the null. Secondly, because the relative strength of various inflammatory biomarkers with regard to AF prediction is not known, our analysis included multiple inflammatory cytokines and soluble receptors. While we believe this approach is supported by biologic plausibility and preferable in light of limited prior data, we recognize that broad inclusion of candidate markers increases the likelihood of observing chance associations. It is important to acknowledge that this study does not establish a causal link between inflammation and AF, and the ability to prevent AF through inflammation suppression remains speculative. AF was not a pre-specified, adjudicated Health ABC Study outcome and we therefore relied upon screening ECGs and ICD-9 coding to identify prevalent and incident disease. It is notable that administrative ICD-9 coding at a large health maintenance organization exhibited 95% sensitivity and 99% specificity for the diagnosis of AF when compared to record review by trained abstractors (30). Nonetheless, we accept that we had a reduced ability to identify participants with AF who were asymptomatic, had paroxysmal disease, or did not seek care. Our findings are unlikely to be secondary to differential access to care, as the association between White race and AF has been replicated in multiple clinic contexts (1, 2, 31, 32) and has been shown to be proportional to European ancestry within a cohort of African-Americans (28). Finally, although we attempted to identify and exclude participants with prevalent AF, we cannot be certain that all individuals with AF at study enrollment were identified. In light of prior investigations that suggest AF itself may contribute to a pro-inflammatory state (33–36), it remains possible that AF was the cause (instead of the consequence) of heightened systemic inflammation. We believe such an “effect-cause” relationship to be unlikely given the long pre-enrollment period over which prevalent AF could be ascertained (up to 6 years) and steady rate of AF diagnoses over our long duration of follow up.

Conclusions

In a population-based sample of older adults, we have demonstrated that systemic inflammatory pathways significantly mediate the heightened risk of AF among Whites compared to Blacks. The higher level of systemic inflammation and concomitant increased AF risk among Whites is not explained by racial differences in abdominal adiposity or the presence of other pro-inflammatory cardiovascular comorbidities such as diabetes, coronary artery disease, and heart failure. Future research aimed at defining and treating the inflammatory pathways unique to AF risk could identify primary prevention therapies relevant to individuals prone to an inflammatory AF subtype.

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Abbreviations List

AF	atrial fibrillation
BMI	body mass index
CRP	C-reactive protein
CT	computed tomography
ECG	electrocardiogram
IL	interleukin
PAI	plasminogen activator inhibitor
SR	soluble receptor
TNF	tumor necrosis factor

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Perspectives

Competency in Medical Knowledge

Despite a lower prevalence of established risk factors, Whites exhibit a substantially increased risk of atrial fibrillation compared to Blacks. Racial differences in inflammation appear to explain a sizeable proportion of the association between White race and atrial fibrillation risk.

Translational Outlook

Additional research aimed at defining and treating the inflammatory pathways unique to AF risk could identify primary prevention therapies relevant to individuals prone to an inflammatory AF subtype.

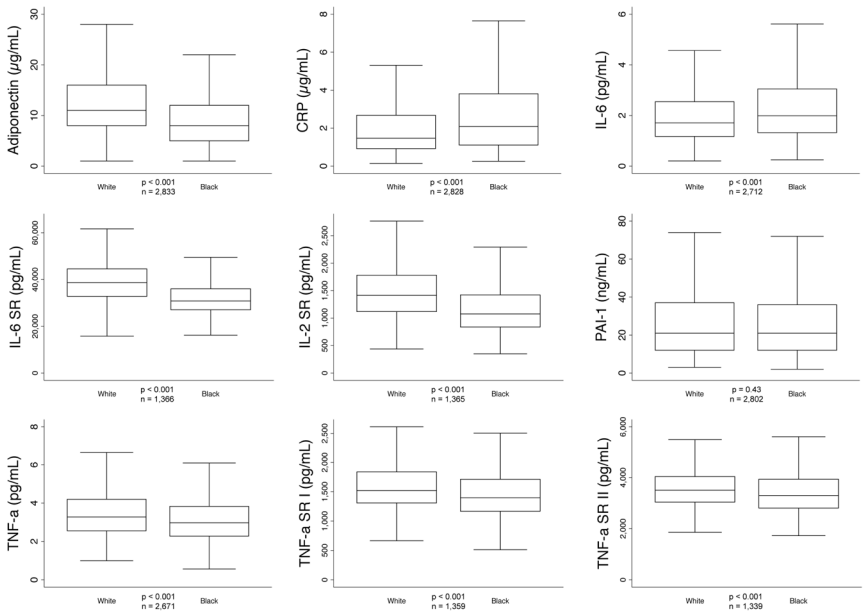

Figure 1. Serum Inflammatory Cytokine Levels by Race

Box plots for the nine measured inflammatory cytokine concentrations stratified by race. P value refers to the comparison of the indicated cytokine concentration between White and Black race. The number of participants with usable cytokine data is listed below each graph (2,864 individuals without prevalent AF were eligible for cytokine analysis, soluble receptor levels were measured in a random subsample of 1,367 participants). Outlier values have been omitted. CRP, C-reactive protein; HR, hazard ratio; IL, interleukin; PAI, plasminogen activator inhibitor; SR, soluble receptor; TNF, tumor necrosis factor.

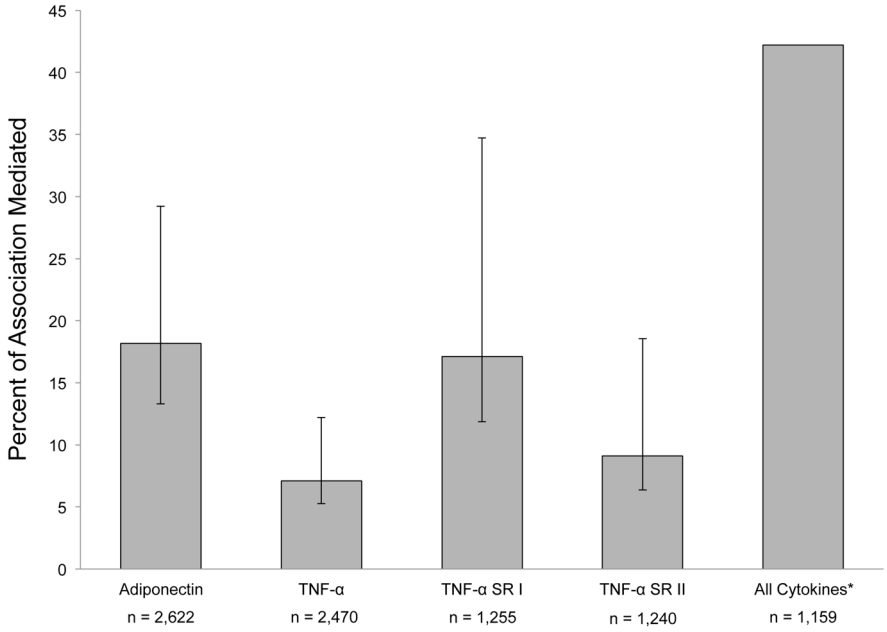

Figure 2. Percent of Race-AF Association Mediated by Inflammatory Cytokines

*The overall percent of association mediated by adiponectin, TNF-α, TNF-α SR I, and TNF-α SR II combined was 42.2% (95% CI 15.2 to 118.9%, p = 0.004, error bars not shown). Percent of association mediated describes the proportion of the race-AF relationship explained by racial differences in the given cytokine concentration. Error bars denote 95% confidence intervals. The number of participants included in each analysis is provided. All mediation analyses are adjusted for race, age, gender, body mass index, tobacco use, alcohol consumption, statin treatment, hypertension, diabetes, coronary artery disease, heart failure, and study site. SR, soluble receptor; TNF, tumor necrosis factor

Table 1

Baseline Characteristics of Health ABC Participants by Race

	Black	White	P value
Age, years, median (IQR)	73 (71–76)	73 (71–76)	0.023
Female Gender, n (%)	668 (57)	767 (48)	< 0.001
Body Mass Index, kg/m^2, mean ± SD	28.6 (5.4)	26.5 (4.1)	< 0.001
Smoking Status			< 0.001
Never, n (%)	530 (45)	700 (44)	
Former, n (%)	454 (39)	783 (49)	
Current, n (%)	192 (16)	104 (7)	
Alcohol Consumption, ≥1 drink/week, n (%)	196 (17)	589 (37)	< 0.001
Statin Use, n (%)	127 (11)	229 (14)	0.005
Hypertension, n (%)	821 (70)	834 (53)	< 0.001
Diabetes, n (%)	246 (21)	160 (10)	< 0.001
Coronary Artery Disease, n (%)	242 (21)	302 (19)	0.22
Heart Failure, n (%)	30 (3)	24 (2)	0.050

Participants with prevalent AF have been excluded. cm, centimeter; IQR, interquartile range; kg, kilogram; m, meter; SD, standard deviation.

Table 2

Association Between Established Risk Factors and Atrial Fibrillation

	Bivariate Model			Multivariate Model*		
Risk Factor	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
White Race	**1.48**	**1.27 to 1.73**	**< 0.001**	**1.55**	**1.30 to 1.84**	**< 0.001**
Age (per year)	1.07	1.05 to 1.10	< 0.001	1.08	1.05 to 1.10	< 0.001
Male Gender	1.47	1.27 to 1.70	< 0.001	1.21	1.04 to 1.42	0.018
BMI (per kg/m^2)	1.03	0.96 to 1.11	0.43	1.05	0.96 to 1.15	0.26
Former Smoker†	1.45	1.24 to 1.69	< 0.001	1.31	1.11 to 1.55	0.001
Current Smoker†	1.20	0.92 to 1.57	0.173	1.35	1.02 to 1.78	0.038
Alcohol Use‡	1.25	1.07 to 1.46	0.005	1.10	0.93 to 1.31	0.26
Statin Use	1.20	0.97 to 1.47	0.089	1.02	0.82 to 1.27	0.87
Hypertension	1.21	1.04 to 1.41	0.014	1.27	1.08 to 1.49	0.003
Diabetes	1.20	0.98 to 1.47	0.073	1.21	0.97 to 1.50	0.085
CAD	1.67	1.41 to 1.97	< 0.001	1.35	1.13 to 1.62	0.001
Heart Failure	2.89	1.94 to 4.31	< 0.001	2.22	1.47 to 3.36	< 0.001

*Adjusted for all variables in Table 2 and study site.

†Compared to never-smokers.

‡Alcohol use defined as ≥ 1 drink per week.

BMI, body mass index; CAD, coronary artery disease, CI, confidence interval; HR, hazard ratio; kg, kilogram; m, meter.

Table 3

Serum Inflammatory Cytokines and Atrial Fibrillation Risk

Inflammatory Cytokine	HR*	95% CI	P value
Adiponectin	1.18	1.07 to 1.31	0.002
CRP	1.10	1.03 to 1.18	0.003
IL-6	1.20	1.10 to 1.30	< 0.001
IL-6 SR	1.13	0.85 to 1.50	0.41
IL-2 SR	1.22	0.99 to 1.49	0.051
PAI-1	1.06	0.98 to 1.14	0.134
TNF-α	1.17	1.02 to 1.35	0.023
TNF-α SR I	1.54	1.16 to 2.05	0.003
TNF-α SR II	1.43	1.09 to 1.87	0.009

*Association between the indicated cytokine and atrial fibrillation, adjusted for race, age, gender, body mass index, tobacco use, alcohol consumption, statin treatment, hypertension, diabetes, coronary artery disease, heart failure, and study site. Inflammatory cytokine concentrations have been log-transformed; the hazard ratio is interpreted as the increased hazard of incident atrial fibrillation for each doubling of cytokine concentration. CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IL, interleukin; PAI, plasminogen activator inhibitor; SR, soluble receptor; TNF, tumor necrosis factor.