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Race-based demographic, anthropometric and clinical correlates of N-terminal-pro B-type natriuretic peptide

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ABSTRACT

Background: Population studies have shown that black race is a natriuretic peptide (NP) deficiency state. We sought to assess whether the effects of age, sex, body mass index (BMI) and estimated glomerular filtration rate (eGFR) on N-terminal-pro-B-type NP (NT-proBNP) levels differ in white and black individuals.
Methods: The study population consisted of a stratified random cohort from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. The study outcomes were the effects of age, sex, BMI and eGFR on NT-proBNP levels independent of socioeconomic and cardiovascular disease factors. Multivariable regression analyses were used to assess the effects of age, sex, BMI and eGFR on NT-proBNP levels in blacks and whites.
Results: Of the 27,679 participants in the weighted sample, 54.7% were females, 40.6% were black, and the median age was 64 years. Every 10-year higher age was associated with 38% [95% confidence interval (CI): 30%–45%] and 34% (95% CI: 22%–43%) higher NT-proBNP levels in whites and blacks, respectively. Female sex was associated with 31% (95% CI: 20%–43%) higher NT-proBNP levels in whites and 28% (95% CI: 15%–45%) higher in blacks. There was a significant linear inverse relationship between BMI and NT-proBNP in whites and a non-linear inverse relationship in blacks. Whites and blacks had a non-linear inverse relationship between eGFR and NT-proBNP. However, the non-linear relationship between NT-proBNP and eGFR differed by race ($p = 0.01$ for interaction).
Conclusions: The association of age and sex with NT-proBNP levels was similar in blacks and whites but the form of the BMI and eGFR relationship differed by race.

1. Introduction

Natriuretic peptides (NPs) are hormones produced by the heart and are commonly utilized in clinical practice as biomarkers to evaluate cardiovascular health [1–4]. We recently described that N-terminal-pro-B-type-NP (NT-proBNP) levels are significantly lower in black compared with white individuals free of cardiovascular and renal disease [5]. This finding that black race is associated with relatively lower natriuretic peptide levels has been reported in multiple other population-based cohorts as well [6–8].

Other than race, NT-proBNP levels differ by 20–40% between groups defined by factors such as age, sex, and body mass index (BMI) [9–12]. Additionally, previous studies have demonstrated that impaired kidney function reduces the clearance of NT-proBNP thereby affecting levels [13–15]. However, information on relationship of NT-proBNP levels with demographic, anthropometric and clinical correlates is available in population cohorts with predominantly white individuals [9–15].

We aimed to examine the differences in the association of age, sex, BMI and eGFR with NT-proBNP levels in black and white individuals in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study [16].

2. Methods

2.1. Study population

The REGARDS study is a large population-based cohort study designed to investigate racial and geographic differences in stroke among adults aged 45 or more [16]. Participants

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other than non-Hispanic whites and blacks were excluded from the study [16]. The details of the study design, inclusion-exclusion criteria, and the recruitment process have been previously described [16]. Briefly, computer-assisted telephone interview followed by an in-home visit was done to enroll a total of 30,239 black and white individuals from 2003 to 2007 [16]. The institutional review boards from each participating center approved the REGARDS study protocol, and all participants provided written informed consent.

A random cohort stratified by age (12% 45–54 years, 38% 55–64 years, 32% 65–74 years, 16% 75–84 years, 2% ≥85 years), sex (45% male; 55% female) and race (42% black; 58% white) was selected for NT-proBNP measurement [5]. Baseline plasma samples from these participants were drawn. Storage of plasma samples as well as validity of laboratory measurements were performed as described previously [17]. The measurement of NT-proBNP was performed using an electrochemiluminescence immunoassay on the automated platform from Roche Diagnostics (Roche Elecsys 2010). The coefficients of variation for intra-assay was <2%, and inter-assay was <5%. For individuals with undetectable NT-proBNP levels ($n = 27$), a value of 5 ng/L (lower limit of detection for the assay) was imputed.

Participants with missing NT-proBNP ($n = 256$) and BMI <18.5 kg/m^2 ($n = 53$) were excluded from our study. We conducted our analyses among the remaining 4106 (27,679 weighted) participants with NT-proBNP levels enrolled in the REGARDS study from January 27, 2003 to October 3, 2007.

2.2. Covariates of interest

Age, sex, race, smoking status, alcohol use, and exercise were self-reported. Body mass index was calculated using weight in kilograms divided by height in meters squared determined by the in-home visit. Systolic blood pressure (BP) was average of two BP measurement 5-minute apart performed on the in-home visit. Aspirin use was self-reported. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP of ≥90 mm Hg, or self-reported current use of anti-hypertensive medication. Diabetes mellitus was defined by self-reported current use of medication or insulin, fasting glucose ≥126 mg/dL (or a non-fasting glucose ≥200 mg/dL among those who did not fast). Total cholesterol ≥240 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, high-density cholesterol ≤40 mg/dL, or self-reported medication use of cholesterol was used to define dyslipidemia. History of stroke or transient ischemic attack (TIA) was self-reported. Atrial fibrillation was defined by self-report or from a presence on the electrocardiogram. History of coronary artery disease was defined if participant reported myocardial infarction, coronary bypass grafting, angioplasty, stenting, or from the evidence of myocardial infarction on the electrocardiogram. Heart failure (HF) was defined as the presence of NT-proBNP levels >300 ng/L (i.e., diagnostic cutoff criteria) [2] as done previously [5]. The electrocardiogram (12-lead) was centrally examined for the presence of left ventricular hypertrophy (LVH), and LVH was determined using Sokolow-Lyon voltage index [18]. Estimated glomerular filtration rate was ascertained from isotope dilution mass spectrometry-traceable serum creatinine measurement using the Chronic Kidney Disease Epidemiology Collaboration equation [19]. Socioeconomic status of REGARDS participants was derived utilizing geocoded addresses to assess neighborhood socioeconomic status (nSES) [20]. The nSES score was calculated, based on six variables [20], 1) median household income; 2) median value of housing unit; 3) proportion of households receiving interest, dividend, or net rental income; 4) proportion of adults aged ≥25 years with a high school diploma; 5) proportion of adults aged ≥25 years with a college degree, and 6) proportion of people employed in executive, managerial, or professional occupations [21]. The nSES score was summarized based on Z score (ranged from −11.8 to 29.0, higher score means higher nSES i.e. most advantaged neighborhood) using the aforementioned variables [21].

2.3. All-cause mortality and cardiovascular mortality

After the baseline visit, semiannual telephonic interviews were conducted of participants or proxies. The date of mortality was determined through examining death certificates, proxies or the national death index [22]. Adjudication of mortality was performed by a committee of physicians by examining death certificates, hospital records, and information provided by proxies. Cardiovascular mortality was established if death from any of the following adjudicated events: myocardial infarction, stroke, sudden death, HF, pulmonary embolism, non-cardiac cardiovascular disease, and other cardiac cause of death.

2.4. Statistical analyses

Statistical analyses were conducted using STATA 15.1 MP (StataCorp LP). Descriptive statistics were used to compare baseline characteristics among black and white individuals. As our study population was derived from a random cohort stratified by age, sex, and race, appropriate weights were implemented (provided by the REGARDS) to represent the overall REGARDS participants. For descriptive statistics, the categorical variables were compared using the Rao-Scott χ^2 test. The graphical methods were used to evaluate the distribution of continuous variables. Continuous variables were reported as median with interquartile interval and were compared using the Mann-Whitney *U* test. As the assumption of normality for NT-proBNP levels was not met, natural log-transformed NT-proBNP levels were used to conduct the statistical analyses.

The scatter plots were used for the assessment of the correlation and outliers between NT-proBNP levels and covariates of interest. Additionally, we performed multivariable linear as well as non-linear regression with robust analytic technique to reduce the influence of outliers [23].

Multivariable linear regression analyses (implementing Tobit models with sampling weights) were performed to assess the associations of age, sex, BMI, and eGFR with NT-proBNP levels in white and black individuals. Additionally, other factors such as smoking, exercise, alcohol use, systolic BP, aspirin use, nSES, and comorbidities such as hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, history of stroke or TIA, coronary artery disease, HF, LVH were included in the multivariable regression model. The covariates included in the multivariable models were selected based on the previous population-based studies demonstrating their association with NT-proBNP levels. [5–8,24–26] Additionally, the multicollinearity among these variables were assessed, and found to have <2 variance inflation factor which is below the threshold of 10. A separate multivariable regression model utilizing NT-proBNP as dependent variable and age (when sex, BMI, and eGFR are exposures), sex (when age, BMI, eGFR are exposure), BMI (when age, sex, eGFR are exposures), eGFR (when age, sex, BMI are exposures), exercise, smoking, alcohol, systolic BP, antihypertensive medication, aspirin use, hyperlipidemia, diabetes, stroke or TIA, atrial fibrillation, coronary artery disease, LVH, nSES, and HF as covariates, was run to assess the association with age, sex, BMI and eGFR among white and black individuals. Data from regression analyses were presented in the β estimates (regression coefficients) with standard errors or percentage difference [calculated using (e^{β}-1)*100]. Additionally, multivariable linear and non-linear (i.e., restricted cubic spline) regression analyses were performed to assess the interaction in the association of NT-proBNP levels with age, sex, BMI, and eGFR by race.

Multivariable-adjusted models with restricted cubic splines were used to assess the non-linear relationship of NT-proBNP levels with age, BMI and eGFR among whites and blacks. The assessment of nonlinearity (testnl command in STATA) and a number of knots for best fit was assessed using the Wald statistics. For the restricted cubic spline models, three knots at 10th, 50th and 90th centile of relevant covariates (age, BMI, or eGFR) were used to plot their relationship with NT-proBNP. The linear relationship was plotted as the linear plot with 95% confidence interval (CI), while the non-linear relationship was plotted using a spline curve to describe the relationship between NT-proBNP levels and age, BMI, and eGFR.

Cox proportional hazard modeling using sampling weights was used to assess effect modification in the relationship of NT-proBNP levels with all-cause and cardiovascular mortality across age, sex, BMI and eGFR categories using multiplicative interaction terms. Multivariable-adjusted models using the following covariates: smoking, exercise, alcohol use, systolic BP, nSES, aspirin use, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, history of stroke or TIA, coronary artery disease, LVH, and HF were used. In these models, we used natural log-transformed NT-proBNP levels as a continuous variable. Separate models utilizing all the aforementioned covariates were generated to assess the association of in NT-proBNP with all-cause and cardiovascular mortality by clinical correlates in both races. A *p*-value of <0.1 was considered significant for interactions.

3. Results

A total of 4106 (27,679 weighted) REGARDS participants with a median age of 64 years [interquartile interval (IQR) 58–71 years] were included. Among these participants, 54.7% were women, and 40.6% were black individuals. Table 1 depicts the baseline characteristics of study participants by race. Black participants were more likely to have higher BMI (30.0 vs. 28.0 kg/m^2, $p < 0.001$) and eGFR (93 vs. 85 mL/min/1.73m^2, $p < 0.001$) than white participants (Table 1). The median NT-proBNP in black participants was significantly lower than in white participants [57(IQR: 27–134) vs. 80 (IQR: 41–178) ng/L, $p < 0.001$). Black participants were more likely to have hypertension and diabetes mellitus than white participants (Table 1). White participants were more likely to have dyslipidemia, atrial fibrillation and history of coronary artery disease than black participants. White participants were more likely to live in more advantaged neighborhood compared with black participants [median Z score (IQR); 1.1 (−2.11, 5.27) vs. −3.0 (−5.20, 0.04), $p < 0.001$] (Table 1).

3.1. Demographic, anthropometric and clinical correlates of NT-proBNP levels

The multivariable-adjusted relationships of NT-proBNP levels with age, sex, BMI and eGFR stratified by race are shown in Table 2. In the multivariable-adjusted model, every 10-year higher age was associated with a 38% (95% CI: 30%–45%) higher NT-proBNP level in whites and 34% (95% CI: 22%–43%) higher level in black participants (Table 2).

Table 1
Baseline characteristics in random cohort participants ($n = 4106$) from REGARDS.

Baseline		Overall (4106)	Whites (2101)	Blacks (2005)	*p*-Value
Weighted frequency		27,679	16,432	11,247	
Age, years		64 (58–71)	65 (59–72)	63 (57–70)	0.254
Female, n (%)		15,127 (54.7)	8172 (49.7)	6955 (61.8)	<0.001
Lifestyle habits	Current smoker, n (%)	3882 (14.1)	2087 (12.8)	1795 (16.0)	0.012
	Current alcohol use, n (%)	14,301 (51.7)	9599 (58.4)	4702 (41.8)	<0.001
	Exercise >4 times a week, n (%)	8495 (31.1)	5388 (33.1)	3107 (28.1)	0.003
BMI, kg/m^2		28 (25–32)	28 (25–31)	30 (26–34)	<0.001
SBP		126 (117–137)	123 (115–134)	129 (120–140)	<0.001
Medication use	Aspirin, n (%)	12,186 (44.0)	8015 (48.8)	4171 (37.1)	<0.001
	Antihypertensive, n (%)	16,346 (59.3)	8299 (50.8)	8047 (71.8)	<0.001
Diabetes, n (%)		5987 (21.9)	2736 (16.9)	3251 (29.2)	<0.001
Dyslipidemia, n (%)		16,014 (58.8)	10,129 (62.5)	5886 (53.2)	<0.001
History of stroke or TIA, n (%)		2778 (10.0)	1571 (9.6)	1207 (10.7)	0.266
Atrial fibrillation, n (%)		2596 (9.6)	1703 (10.6)	893 (8.1)	0.024
Coronary artery disease, n (%)		4773 (17.5)	3205 (19.7)	1568 (14.2)	<0.001
Heart Failure, n (%)		7454 (26.9)	4424 (26.9)	3030 (26.9)	0.990
Left ventricular hypertrophy, n (%)		2667 (9.8)	1174 (7.2)	1493 (13.5)	<0.001
nSES		−0.8 (−3.78, 3.14)	1.1 (−2.11, 5.27)	−3.0 (−5.20, 0.04)	<0.001
NT-proBNP, ng/L		71 (35–161)	80 (41–178)	57 (27–134)	<0.001
eGFR, mL/min/1.73m^2		88 (73–98)	85 (72–94)	93 (75–107)	<0.001

Continuous variables are shown as median and interquartile interval and were compared using Mann-Whitney *U* test; categorical variables are shown as n (%) and were compared using Chi-square test.
Abbreviations: BMI, indicates body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; nSES: neighborhood socioeconomic status at census block level; REGARDS, REasons for Geographic And Racial Differences in Stroke Study; SBP, indicates systolic blood pressure; and TIA, Transient ischemic attack.

The relationship of NT-proBNP level and age was linear in both races. Fig. 1 represents the relationship of NT-proBNP with age stratified by race in the multivariable-adjusted model. There was a progressive increase in NT-proBNP with increasing age categories in white and black individuals ($P_{trend} < 0.001$ for both races) (Table 2). Compared with males, females had 31% (95% CI: 20% to 43%) higher NT-proBNP levels in whites and 28% (95% CI: 15%–45%) higher in blacks (Table 2). Furthermore, we observed a significant interaction in the relationship between NT-proBNP and BMI by race in the linear multivariable-adjusted models (p for interaction = 0.06). In the non-linear multivariable-adjusted models, we observed a significant interaction in the association of NT-proBNP with eGFR by race (p for interaction = 0.012). We did not observe any interactions in the association between NT-proBNP and age & sex by race in both linear as well as non-linear multivariable regression models.

3.2. Assessment of non-linear relationship of NT-proBNP levels with BMI and eGFR

Using multivariable adjusted restricted cubic spline modeling, we observed a significant non-linear relationship between NT-proBNP and BMI among black participants (p for nonlinearity<0.001) but not in whites (p for nonlinearity = 0.06) (Fig. 2, Panel A). Fig. 2, Panel A suggests NT-proBNP had an inverse relationship with BMI until ~30 kg/m^2 (β-estimate = −0.05, 95% CI: −0.08 to −0.03, $p = 0.005$), and a positive relationship with BMI >30 kg/m^2 among black participants (β-estimate = 0.02, 95% CI: 0.01 to 0.02, $p = 0.001$). Adjusted restricted cubic spline modeling (Fig. 2, Panel B) showed that the relationship between NT-proBNP levels and eGFR was non-linear among white (p for nonlinearity = 0.008) and black (p for nonlinearity<0.001) participants. We observed that the relationship between NT-proBNP and eGFR differed

Table 2
Demographic, Anthropometric and clinical correlates of plasma NT-proBNP levels stratified by race: Multivariable Regression Results.

Models	Whites		Blacks	
	β coefficient (SE)	Percentage difference (95% CI)	β coefficient (SE)	Percentage difference (95% CI)
Age (per 10 years)	0.32 (0.03)[#]	38 (30 to 45)	0.29 (0.03)[#]	34 (22 to 43)
45–55 years		Referent		Referent
55–65 years	0.23 (0.06)[#]	26 (11 to 42)	0.18 (0.08)[*,**]	20 (2 to 42)
65–75 years	0.67 (0.07)[#]	95 (72 to 125)	0.60 (0.09)[#]	82 (54 to 128)
>75 years	0.97 (0.08)[#]	164 (127 to 206)	0.83 (0.10)[#]	129 (90 to 177)
Female	0.27 (0.05)[#]	31 (20 to 43)	0.25 (0.06)[#]	28 (15 to 45)
Continuous BMI (1 kg/m^2)	−0.022 (0.01)[#]	−2.2 (−3.0 to −1.3)	−0.011 (0.005)[*]	−1.1 (−2.0 to −0.01)
Continuous eGFR (per 10 mL/min/1.73 m^2)	−0.12 (0.02)[#]	−11 (−14 to −8)	−0.12 (0.02)[#]	−11 (−14 to −9)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SE, standard error.
All β-estimates were generated using multivariable linear regression models using natural log-transformed NT-proBNP as dependent variable and respective covariates as the independent variable. Different models were used to generate β-estimates for whites and blacks. Values shown are β-estimates (SE), which are on the log NT-proBNP scale or percentage change with 95% confidence interval.
Multivariable model adjusted for age (when sex, BMI, and eGFR are exposures), sex (when age, BMI, eGFR are exposure), body mass index (BMI) (when age, sex, eGFR are exposures), estimated glomerular filtration rate (eGFR) (when age, sex, BMI are exposures), exercise, smoking, alcohol, systolic blood pressure, antihypertensive medication, aspirin use, hyperlipidemia, diabetes, stroke, transient ischemic attack, atrial fibrillation, coronary artery disease, left ventricular hypertrophy, neighborhood socioeconomic status at census block level, and heart failure.
[*] $p < 0.05$.
[**] $p < 0.01$.
[#] $p < 0.001$.

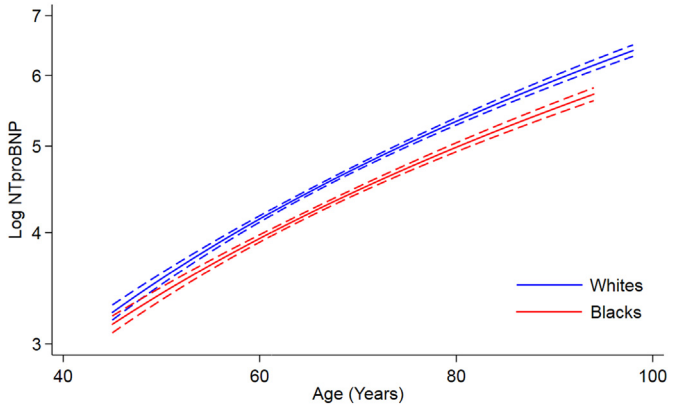

Fig. 1. Racial differences in relationship of plasma NT-proBNP levels with age in multivariable linear regression models. Multivariable linear regression models using natural log-transformed NT-proBNP as the dependent variable and Age as the independent variable were used. Values shown are predicted log NT-proBNP levels with 95% confidence interval. Multivariable Model adjusted for sex, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medication, aspirin use, hyperlipidemia, diabetes, estimated glomerular filtration rate, stroke, transient ischemic attack, atrial fibrillation, coronary artery disease, left ventricular hypertrophy, neighborhood socioeconomic status at census block level, and heart failure.

between races (Fig. 2, Panel B). Blacks with decreasing eGFR (below <60 mL/min/1.73m^2), had a greater increase in NT-proBNP levels as compared with whites with decreasing eGFR.

Among white participants, there was a significant interaction between NT-proBNP and sex for all-cause ($p = 0.03$) and cardiovascular mortality ($p = 0.09$). For every 1-unit increment in log NT-proBNP, there were 41% and 81% higher risk of death for white men [hazard ratio (HR): 1.41; 95% CI: 1.16–1.70, $p < 0.001$] and women (HR: 1.81; 95% CI: 1.37–2.39, $p < 0.001$), respectively (Supplemental Table). The difference in the risk of all-cause mortality by sex among white participants was driven by the differential strength of association between NT-proBNP and cardiovascular mortality in women and men (HR: 3.02; 95% CI: 1.76–5.22, $p < 0.001$ for women and HR: 1.92; 95% CI: 1.34–2.74 for men, $p < 0.001$) (Supplemental Table). However, among black participants, the association of NT-proBNP with all-cause mortality was similar in men and women (Supplemental Table). The association of NT-proBNP levels with all-cause and cardiovascular mortality did not differ by age, BMI, and eGFR categories among white and black individuals (interaction $p > 0.1$ for both races).

4. Discussion

In participants from the REGARDS study, increasing age and female sex were positively associated with NT-proBNP levels in both white and black individuals. While rising BMI and eGFR were inversely associated with NT-proBNP levels, the form of these relationships differed by race. The association between NT-proBNP levels and all-cause mortality differed by sex in whites and not in blacks. Among white participants, higher NT-proBNP levels was associated with a greater risk of all-cause mortality in females compared with males.

Among white and black participants, a similar rise in NT-proBNP levels was observed with every 10-year higher age (i.e., ~35%). The relationship of NT-proBNP levels with age has been previously reported, albeit in white participants [10,11,27]. Mechanistically, higher NT-proBNP levels with age may be a consequence of the increasing prevalence of subclinical cardiovascular disease indicating greater wall stress (i.e., a reflection of the response arm of the NP system) [10,11,27]. Population based-studies have observed an increase in NT-proBNP levels ranging from 20% to 70% with every 10-year increase in age [10,11,27]. Additionally, cohort studies by Gupta et al. which have specifically examined the racial disparities in NT-proBNP levels, have shown that race does not modify the relationship of NT-proBNP with age [6–8]. Similarly, our finding on lack of interaction by race in the association of NT-proBNP levels with age, suggest that an increase in NT-proBNP levels with normal aging is independent to individuals' race.

Our findings are consistent with the previous reports that females have ~30% higher NT-proBNP levels than males [27]. The difference in NT-proBNP levels between males and females could be due to the stimulatory effect of female sex hormones and the inhibitory effect of male sex hormones on NP gene expression/release [28–31]. Sex-based differences in myocardial gene expression have been described previously in organ donors with no prior cardiovascular disease [32]. Additionally, our findings suggest that race does not modify the effect of sex on NT-proBNP levels which has been previously noted [6–8]. We noted a differential relationship of NT-proBNP with all-cause and cardiovascular mortality by sex in whites which was consistent with previous studies [33,34]. However, we did not observe any modification in the association between NT-proBNP and all-cause mortality by sex in black

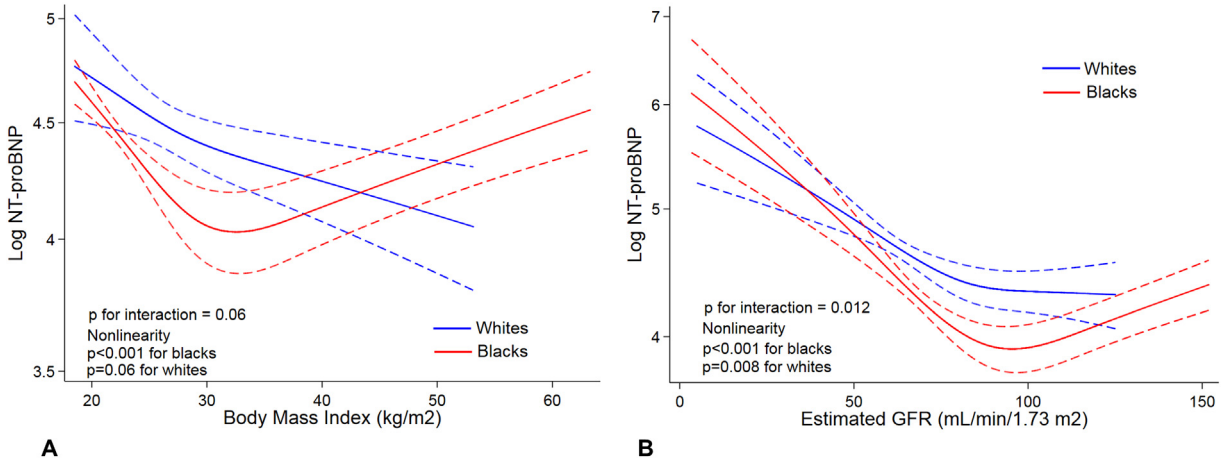

Fig. 2. Relationship of plasma NT-proBNP Levels with body mass index (Panel A) and estimated glomerular filtration rate (Panel B) in white and black individuals. Multivariable restricted cubic spline relationship between NT-proBNP and body mass index (Panel A) and between NT-proBNP and estimated glomerular filtration rate (Panel B) in whites (blue color) and blacks (red color). Values shown are predicted log NT-proBNP levels with 95% confidence interval. Multivariable Model adjusted for age, sex, exercise, smoking, alcohol, body mass index, systolic blood pressure, antihypertensive medication, aspirin use, hyperlipidemia, diabetes, estimated glomerular filtration rate, stroke, transient ischemic attack, atrial fibrillation, coronary artery disease, left ventricular hypertrophy, neighborhood socioeconomic status at census block level, and heart failure.

individuals. Further studies will be required to investigate pathophysiological basis of these findings.

In white participants, increasing BMI was associated with a linear decrease in NT-proBNP levels. Multiple epidemiological studies have previously reported an inverse linear relationship in whites between circulating NP levels and BMI [35–37]. Impared synthesis [38] or diminished myocardial release [39] may be the reasons behind the observed relationship between NT-proBNP levels and BMI. Contrary to our and findings from the other cohorts, the Atherosclerosis Risk in Communities (ARIC) study observed a U-shaped association between NT-proBNP and BMI among white individuals [40]. Smaller proprortion of white individuals with high BMI (>35 kg/m^2) and limited statistical power in our study may be the reasons behind the differences of our finding from the ARIC study [40].

We noted a non-linear (i.e., U-shaped) inverse relationship between NT-proBNP and BMI among black participants. The aforementioned finding is concordant with the population-based studies including black individuals [40,41]. Among black individuals, we observed that the relationship of BMI and NT-proBNP flattened at ~30 kg/m^2, while the results from the Jackson Heart Study showed this relationship was leveled at ~40 kg/m^2 [41]. The ARIC study showed a non-linear J-shaped relationship between NT-proBNP and BMI among blacks [40]. The observed difference in the shape of the relationship between NT-proBNP and BMI by race in our investigation may be explained by the presence of higher number of severely obese (>35 kg/m^2) black ($n = 357$) individuals. Furthermore, it has been proposed that an increase in NT-proBNP levels in the severely obese individuals may be a reflection of underlying increased risk of cardiovascular disease [40].

A non-linear relationship between NT-proBNP levels and eGFR was observed which was significantly different by race. We observed a greater increase in NT-proBNP levels among blacks with eGFR <60 mL/min/1.73m^2 as compared with whites. Our population-based investigation also adds to the existing literature regarding the association of NT-proBNP levels with eGFR [42,43]. Similar to the previous finding, we noted plasma NT-proBNP levels increased exponentially with eGFR <90 mL/min/1.73m^2 in both races [42,43]. The aforementioned relationship was independent of other confounding variables such as HF as noted in our multivariable-adjusted analyses. Investigators of Multi-Ethnic Study of Atherosclerosis have reported that the relationship between NT-proBNP and eGFR did not differ by race [6]. Contrary, we observed a greater rise in NT-proBNP levels among black individuals with impaired kidney function. NT-proBNP is primarily cleared through excretion by the kidneys [43,44]. Additionally, decrease in circulating NT-proBNP levels after hemodialysis furthered the aformentioned notion for NT-proBNP clearance as the primary mechanism for this association [45]. This observation suggests that any alteration in renal function can increase circulating NT-proBNP levels. Our observation that NT-proBNP levels in blacks are higher than whites with a similar degree of renal dysfunction (eGFR <60 mL/min/1.73m^2) may suggest that the rate of clearance of NT-proBNP from the circulation is race dependent and is an area of future investigation. Risk prediction models utilizing NT-proBNP levels need to be adjusted for impairment in renal function, especially among black individuals which calls for different cut-off values of NT-proBNP levels for HF in chronic kidney disease population.

To the best of our knowledge, no study has formally examined the association of NP levels with demographic, anthropometric, and clinical correlates stratified by race. We report for the first time in a population-based cohort with a sizeable number of black individuals that the association of NT-proBNP with BMI and eGFR differs by race. Population-based studies have suggested an inverse relationship between clinical components of metabolic syndrome (i.e., high blood glucose, dyslipidemia) and NT-proBNP levels [26,46–48]. We adjusted for metabolic syndrome variables and other known clinical covariates associated with NT-proBNP levels while reporting the strength and form of race-stratified relationship of NT-proBNP levels with age, sex, BMI, and eGFR.

4.1. Limitations

We acknowledge that our study has limitations. The characterization of the race was from self-report instead of using genetic ancestry information markers. The REGARDS study consisted of white and black individuals who were 45 years and older, so our results cannot be generalized to individuals with age <45 years and other racial or ethnic populations. We performed linear and non-linear multivariable regression analyses to assess the effects of age, sex, BMI and eGFR on NT-proBNP levels by race. Linear regression is simple to perform, has easy interpretability, and provides the best fit line with minimum errors. However, linear regression loses its applicability when the relationship is non-linear between outcome and predictor variable as well as data are non-normal. Non-linear regression can be applied when the relationship between outcome and predictor variable is non-linear. Nonetheless, non-linear regression parameters are hard to interpret and more prone to outliers than linear regression. As we did not have non-invasive imaging such as echocardiography data for cardiac structure and/or function to characterize the etiology of HF or presence of overt cardiomyopathy, we used a guideline-recommended diagnostic approach i.e., NT-proBNP >300 ng/L for HF diagnosis (rule out criteria) and adjusted for HF as a covariate while examining the relationship of NT-proBNP levels with age, sex, BMI, and eGFR. Using the previous literature, we tried to include all the known factors that can affect NP levels. However, the issue of unmeasured and unidentified confounders is likely to remain, especially with increasing age and decreasing eGFR categories. Additionally, the multiple comparisons and the use of self-reported cardiovascular disease may be an issue. Our study is based on plasma NT-proBNP levels at baseline. Serial measurements may provide additional information on the relationship of NT-proBNP with age, sex, BMI, and eGFR categories among black and white individuals [29]. It is also possible that there are differential effects by NP type such as mature B-type NP, N-terminal pro-atrial NP and mature atrial NP which are not available in REGARDS participants. Finally, our study depicts the association of age, sex, BMI, and eGFR on NT-proBNP levels by race and no causal inferences can be drawn from this work. The results of our study are not able to establish a direct pathophysiological link between NP levels and these variables. Furthermore, the non-linear relationship between NT-proBNP and BMI (in blacks) and eGFR (in both races) supports the hypothesis that the relationship between NT-proBNP levels and BMI and eGFR is more complex than expected.

5. Conclusions

In summary, we have found in a large population-based study among white and black individuals that the shape and strength of the relationship of age and sex with NT-proBNP levels are similar in both races. However, the shape of the relationship between BMI and NT-proBNP levels is different by race (linear in whites vs. non-linear in blacks). Furthermore, the relationship between eGFR and NT-proBNP levels differed by race with a greater increase in NT-proBNP levels with impaired kidney function in blacks. The aforementioned findings indicate pathophysiological complexity in the relationship between NT-proBNP levels and BMI and eGFR.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.034.

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