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Differences in Natriuretic Peptide Levels by Race/Ethnicity (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Natriuretic peptides (NP) are cardiac-derived hormones with favorable cardiometabolic actions. Low NP levels are associated with increased risks of hypertension and diabetes mellitus, conditions with variable prevalence by race/ethnicity. Heritable factors underlie a significant proportion of the inter-individual variation in NP concentrations, but the specific influences of race and ancestry are unknown. In 5,597 individuals (40% White, 24% Black, 23% Hispanic, and 13% Chinese) without prevalent cardiovascular disease at baseline in the Multi-Ethnic Study of Atherosclerosis, multivariable linear regression and restricted cubic splines were used to estimate differences in serum N-terminal pro B-type natriuretic peptide (NT-proBNP) levels according to race/ethnicity and ancestry. Ancestry was determined using genetic ancestry informative markers. NT-proBNP concentrations differed significantly by racial/ethnicity (Black, median 43 pg/ml [IQR 17–94], Chinese 43 [17–90], Hispanic 53 [23–107], White 68 [34–136]; $P = 0.0001$). In multivariable models, NT-proBNP was 44% lower (95% CI, –48 to –40) in Black and 46% lower (–50 to –41) in Chinese, compared with White individuals. Hispanic individuals had intermediate concentrations. Self-identified Blacks and Hispanics were the most genetically admixed. Among self-identified Black individuals, a 20% increase in genetic European ancestry was associated with 12% higher (1 to 23%) NT-proBNP. Among Hispanic individuals, genetic European and African ancestry were positively and negatively associated with NT-proBNP levels, respectively. In conclusion, NT-proBNP levels differ according to race/ethnicity, with the lowest concentrations in Black and Chinese individuals. Racial/ethnic differences in NT-proBNP may have a genetic basis, with European and African ancestry associated with higher and lower NT-proBNP concentrations, respectively.

Keywords

natriuretic peptide; race; admixture; genetics

Introduction

Natriuretic peptides (NP) are cardiac-derived hormones with beneficial cardiometabolic effects including natriuresis, diuresis, vasodilation, insulin sensitivity, and lipolysis.^{1,2} Animal and human studies demonstrate that relative NP deficiencies are associated with the development of salt-sensitive hypertension, insulin resistance, diabetes mellitus, and obesity.^{3–8} These cardiovascular risk factors disproportionately affect certain races/ethnicities, suggesting that relatively low NP concentrations may contribute to racial differences in susceptibility to cardiometabolic disease.^{9,10} However, whether NPs concentrations differ between racial/ethnic groups, with relatively low concentrations corresponding with those groups carrying the highest burden of cardiometabolic disease, has not been completely characterized.^{11–13} Furthermore, a substantial proportion of the inter-individual variation in circulating NP concentrations has been attributed to genetic factors.¹⁴ Whether genetic ancestry is also associated with NP concentrations has not been comprehensively examined. In the Multi-Ethnic Study of Atherosclerosis (MESA), we tested whether N-terminal pro B-type NP (NT-proBNP) concentrations differed between White, Black, Chinese, and Hispanic individuals. We also examined the associations between genetic ancestry and NT-proBNP concentrations.

Methods

MESA is an ongoing, prospective observational study of subclinical cardiovascular disease and risk factors, for which detailed methods have been previously published.¹⁵ Briefly, between July 2000 and July 2002, 6,814 asymptomatic men and women aged 45 to 84 years and without prevalent cardiovascular disease were recruited from 6 communities in the United States (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA). Each site enrolled an approximately equal number of men and women according to pre-specified age and race/ethnicity proportions (39% White, 28% Black, 22% Hispanic, and 12% Chinese). The final study cohort for this analysis included 5,597 individuals in whom NT-proBNP was measured at baseline, as described below.¹⁶ Institutional review boards from each site approved the study and informed consent was obtained from all participants.

Race/ethnicity was self-reported as White, Chinese, Black, or Hispanic. Conventional definitions for hypertension (blood pressure > 140/90 mmHg or anti-hypertensive medication use) and diabetes mellitus (fasting blood glucose ≥ 126 mg/dL or anti-diabetic medication use) were used. Heart rate, blood pressure, height and weight were measured using standardized protocols. Education and income were self-reported. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (μIU/ml) x fasting glucose (mmol/l)/22.5.¹⁷ Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation and urinary albumin/creatinine was measured using nephelometry and the rate Jaffe reaction (Clinical Chemistry Laboratory, Fletcher Allen Health Care, Burlington, VT).¹⁸ Left ventricular mass and ejection fraction were calculated from offline analysis of short-axis, breath-hold, electrocardiographic-gated cine cardiac magnetic resonance images obtained on 1.5-T MRI scanners (Siemens Medical Systems, Malvern, PA; GE Healthcare, Wauwatosa, WI) in a subset of participants (n=4,162).¹⁶

Serum NT-proBNP concentrations were determined from samples drawn at baseline that were frozen and stored at -70°C . All measurements were performed in a CLIA certified laboratory at the Veteran's Affairs San Diego Healthcare System (La Jolla, CA), using the Elecsys 2010 proBNP platform (Roche Diagnostics, Indianapolis, IN). The intra- and inter-assay coefficients of variation were: at 175 pg/ml, 2.7% and 3.2%; at 355 pg/ml 2.4% and 2.9%; at 1,068 pg/ml, 1.9% and 2.6%, and at 4,962 pg/ml 1.8% and 2.3%. The limits of detection were 5 and 35,000 pg/ml.¹⁶

Genotyping methods for estimating genetic ancestry have previously been reported in MESA.^{19,20} Briefly, two sets of ancestry proportion estimates were computed; the first included individuals who self-reported race/ethnicity as either White or Black. These estimates were computed assuming 2 ancestral populations (central European and West African Yoruban) using 300 markers. The second set of ancestry estimates was computed based upon several genome-wide admixture panels for Hispanic and Chinese individuals. Panels 1 and 2 were then combined into a single list, which were examined on the Affymetrix AFFY 6.0 chip. Ancestry proportion was estimated from 406 identified SNPs using the software ADMIXMAP, which allows for the direct inclusion of ancestral allele frequencies.

For statistical analyses, participants were categorized according to self-reported race/ethnicity. Summary statistics were calculated as counts (%) and medians (25th, 75th percentiles) for categorical and continuous data, respectively. Unadjusted NT-proBNP concentrations were compared across groups using the Kruskal-Wallis test. The frequency of NT-proBNP levels below detection limit were compared between racial/ethnic groups using the χ^2 test. NT-proBNP values were natural log transformed prior to entry into regression models. Sequential multivariable-adjusted linear regression models were used to assess the associations between race/ethnicity (independent) and natural log transformed NT-proBNP concentrations (dependent). The multiplicative effect (% difference) on NT-proBNP concentrations was estimated as $(e^{\beta}-1) \times 100$, where β is the coefficient from linear regression models. Covariates in multivariable-adjusted models were selected a priori and included: age, sex, anti-hypertensive medication use, diabetes mellitus, heart rate, systolic blood pressure, BMI, eGFR, urine albumin to creatinine ratio, LDL cholesterol, triglycerides, annual household income, education, left ventricular ejection fraction and left ventricular mass. In additional analyses, HOMA-IR was included in multivariable models among individuals without diabetes mellitus. Interaction terms to assess for effect modification by age, sex, hypertension, diabetes mellitus, obesity, and chronic kidney disease were also included. Within each self-reported race/ethnicity, multivariable linear regression and restricted cubic spline analyses with three knots were used including proportion genetic ancestry as the primary independent variable with adjustment for covariates listed above. The number of knots was selected based upon the model that produced the lowest Akaike Information Criterion (AIC). All analyses were performed using Stata 13.1 (Stata Corp., College Station, TX). For all statistical tests, 2-sided *P* values <0.05 were considered significant without adjustment for multiple testing.

Results

Of the 6,814 MESA baseline participants, 1,217 were excluded due to lack of NT-proBNP measures. Compared with the excluded, the cohort of included participants ($n = 5,597$) was slightly older (median 63 vs. 61 years), with fewer women (51% vs. 59%), fewer Blacks (24% vs. 44%), and less hypertension (48% vs. 52%), while other baseline characteristics, such as diabetes, renal function, LV mass index, and LVEF were similar (data not shown).

The included study sample was 40% White, 24% Black, 23% Hispanic, and 13% Chinese (Table 1). Hypertension was most common among Blacks, while diabetes mellitus was most common among Black and Hispanic individuals. Chinese individuals had the lowest BMI, but were more insulin resistant compared with White individuals. Hispanic individuals were the most insulin resistant. Unadjusted NT-proBNP concentrations were lowest in Black (median 43 [25th–75th percentiles, 17 – 94] pg/ml) and Chinese individuals (43 [17 – 90]), highest among White individuals (68 [34 – 136]), and intermediate among Hispanics (53 [23 – 107]) ($P = 0.0001$). NT-proBNP concentrations below the limit of detection (< 5 pg/ml) were also more common among Black and Chinese individuals compared with Whites and Hispanics, $P < 0.001$.

In multivariable models, adjusted NT-proBNP concentrations were 46% lower (95% CI: –50 to –41) in Black compared with White individuals (Figure 1). Adjustment for insulin resistance did not substantially attenuate the difference in NT-proBNP concentrations between Black and White participants (Table 2). NT-proBNP concentrations were 41% lower (95% CI: –46 to –35) in Chinese compared with White individuals (Figure 1). Hispanic individuals also had lower NT-proBNP concentrations (–27%, 95% CI: –35 to –20) compared with Whites. Interaction terms to test for modification of the association between race/ethnicity and NT-proBNP concentrations were not significant for age, sex, hypertension, diabetes, obesity, or chronic kidney disease ($P > 0.05$ for all).

The analyses were repeated with restriction of the study sample to individuals with detectable levels of NT-proBNP (i.e. > 5 pg/ml), and the racial/ethnic differences persisted (Black: 35% lower [95% CI: –40 to –30]; Chinese: 32% lower [–38 to –26]; Hispanic 23% lower [–29 to –16] compared with White individuals). In the subset of healthy individuals ($n = 784$), defined as being lean ($\text{BMI} < 25 \text{ kg/m}^2$), without diabetes mellitus, hypertension, or renal dysfunction, and having LVEF $\geq 55\%$, NT-proBNP concentrations remained significantly lower in Black, Chinese, and Hispanic compared with White individuals (Black: –44% [95% CI: –57 to –27]; Chinese: –48% [–58 to –36]; Hispanic –34% [–49 to –14]).

Among the 5,434 (97%) participants in whom genetic ancestry data were available, self-reported White and Chinese participants had the least genetic admixture, while Hispanic and Black individuals were the most genetically admixed (Table 3). In multivariable-adjusted linear regression analyses, among self-reported Blacks, a 20% increase in the proportion of European ancestry was associated with an 11.6% increase (95% CI: 1.1 to 23.3) in NT-proBNP concentration. Similarly, among self-reported Hispanic individuals, a 20% increase in European ancestry was associated with 7.4% (0.3 to 15.1) higher NT-proBNP levels. In

contrast, a 20% increase African ancestry was associated with 10.4% (95% CI: -18.9 to -1.1) and 10.0% (-16.2 to -3.3) lower NT-proBNP levels among self-reported Black and Hispanic participants, respectively. Chinese ancestry was not associated with NT-proBNP concentrations among Hispanic individuals (-9.8% [95% CI -23.7 to 6.7] per 20% increase).

In multivariable-adjusted restricted cubic spline analyses, increasing proportion of European ancestry among Blacks was associated with higher NT-proBNP concentrations (Figure 2A). Among self-reported Hispanic participants, increasing proportion of European ancestry was also associated with higher NT-proBNP levels, although beyond approximately 60% European ancestry, NT-proBNP levels appeared to plateau (Figure 2B). By contrast, increasing African ancestry appeared to associate with lower NT-proBNP concentrations among both self-reported Blacks and Hispanic individuals (Figure 2, C and D).

Discussion

Our findings demonstrate racial/ethnic differences in NT-proBNP concentrations that may have a genetic basis. Using data from a large, community-based, multi-ethnic study, we found that NT-proBNP concentrations were lowest among Black and Chinese individuals, intermediate in Hispanics, and highest among White individuals. These differences were independent of other factors previously reported to be associated with NP concentrations, including insulin resistance, obesity, left ventricular mass, ejection fraction, and renal function. Concordantly, we also demonstrated consistent relationships between genetic ancestry and NP concentrations, with greater European ancestry associated with higher NT-proBNP concentrations, and greater African ancestry linked to lower concentrations. These findings not only support the primary result of racial/ethnic differences in NT-proBNP levels, but also support a possible genetic basis. Because NP deficiencies promote hypertension and diabetes mellitus,³⁻⁸ our findings raise the possibility that reduced NP activity contributes to racial/ethnic disparities in susceptibility to these as well as related cardiometabolic disorders.

Circulating NP concentrations are lower in individuals with diabetes mellitus and insulin resistance.²¹⁻²³ These conditions are more common among Black, Chinese, and Hispanic, than White individuals. In this study, even with adjustment for these cardiometabolic comorbidities and hemodynamic factors, NP concentrations were significantly lower in Black, Chinese, and Hispanic compared with White individuals. The magnitude of differences in NT-proBNP concentrations between White individuals and the other racial/ethnic groups (26-43% lower) was similar to that previously reported among obese (6-20% lower) and insulin resistant (10-30% lower) individuals, suggesting the observed racial/ethnic differences in NP concentrations are likely physiologically significant.^{21,23} Furthermore, in the ARIC study and MESA, it has previously been demonstrated that lower NP concentrations, even within the range that would be considered "normal" or not diagnostic of heart failure and comparable to NT-proBNP concentrations observed in this analysis, are associated with increased risk of diabetes mellitus in follow-up.^{7,8}

Although the precise mechanisms underlying the racial/ethnic differences in NT-proBNP concentrations are incompletely understood, prior studies indicate that a substantial proportion (~40%) of the inter-individual variation in NP concentrations among community-based subjects is attributable to heritable factors.¹⁴ Our findings in MESA may provide further support for a genetic contribution to NP concentrations. We observed a “dose-response” relationship between genetic ancestry and NT-proBNP concentrations, such that European ancestry was positively associated with NT-proBNP concentrations, while African ancestry was negatively associated. These contrasting associations suggest multiple variants may influence NP concentrations and these may differ by ancestry.

Prior studies provide some evidence to support a genetic basis for racial/ethnic variation in NP concentrations. For instance, micro-RNA 425 negatively regulates ANP production by binding to a NP precursor A (*NPPA*) gene variant in the 3' untranslated region (rs5068 A/G); this variant is more common among White compared with Black individuals and is associated with higher circulating atrial NP concentrations, lower blood pressure, less hypertension, and a favorable metabolic profile.^{6,10,24,25} By contrast, Blacks are more likely to carry non-synonymous variants in the *CORIN* gene compared with White individuals.²⁶ Corin is a cardiac serine protease that cleaves NP prohormones into biologically active and inactive components. Individuals with certain *CORIN* variants are at increased risk for hypertension and ventricular hypertrophy.^{26,27} Among Chinese individuals, the rs5063 variant in the coding region of *NPPA* leads to an amino acid change from valine to methionine and is associated with lower blood pressure.²⁸ Genetic variants in the NP clearance receptor (*NPR-C*) have also been associated with hypertension in Caucasian and Asian individuals.^{29,30}

Although we examined a large, well-phenotyped, multi-ethnic population without prevalent cardiovascular disease, limitations should be noted. Race and ethnicity were self-reported, which may result in misclassification bias; however, our results were similar when NT-proBNP concentrations were examined in relation to genetic ancestry. A small minority of participants had NT-proBNP concentrations below detection limit. However, racial/ethnic differences persisted even when restricted to individuals with detectable NT-proBNP concentrations. The precise mechanisms contributing to racial/ethnic differences in NP concentrations could not be determined; however, the ancestry findings suggest a possible genetic basis. Identifying specific variants that influence NP levels and whose frequencies vary by race or ethnic group is an area for future investigation. In estimating genetic ancestry, there may be misclassification bias due to the inability to account for local ancestry.²⁰ The small proportion of Chinese ancestry among self-reported White, Black, and Hispanic individuals limited power to assess the association between Chinese ancestry and NT-proBNP levels. Despite adjustment for multiple factors that may influence NP concentrations, there may be residual confounding. Finally, in this cross-sectional analysis we cannot define a causal association between low NP concentrations and incident cardiometabolic disease. However, it has previously been demonstrated in both animal and human studies that low NP concentrations are associated with increased risk for diabetes mellitus, and genetic variants in the NP system yielding lower NP concentrations result in hypertension.^{6–10}

In conclusion, NP concentrations varied by race/ethnicity, which appeared to have a genetic basis. Whether augmentation of the NP system is an efficacious strategy for the prevention of cardiometabolic disease among individuals with relatively low NP concentrations warrants further investigation.

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Figure 1. Multivariable adjusted percent differences in serum N terminus pro B type natriuretic peptide concentrations by self-reported race/ethnicity in the Multi-Ethnic Study of Atherosclerosis

Data presented as point estimate (95% confidence interval). Adjusted for age, sex, anti-HTN medication use, diabetes mellitus, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, urine albumin to creatinine ratio, low density lipoprotein cholesterol, triglycerides, education, income, left ventricular mass, and left ventricular ejection fraction. $P < 0.001$ for all race/ethnic group comparisons with white individuals.

Figure 2. Relationships between genetic ancestry and N terminus pro B type natriuretic peptide concentrations in the Multi-Ethnic Study of Atherosclerosis

Multivariable-adjusted restricted cubic splines with data presented as point estimate (solid line) and 95% confidence interval (dashed lines). The histograms display the distribution of genetic ancestry within a self-reported race/ethnic group. All analyses adjusted for age, sex, anti-HTN medication, diabetes mellitus, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, urine albumin to creatinine ratio, low density lipoprotein cholesterol, triglycerides, education, income, left ventricular mass, and left ventricular ejection fraction. Genetic ancestries were included as covariates as follows: Panel A = European, Hispanic, and Chinese; Panels B & D = European, African, and Chinese; Panel C = African, Hispanic, and Chinese.

Table 1

Characteristics of Multi-Ethnic Study of Atherosclerosis participants by race/ethnicity.

	White	Chinese	Black	Hispanic
	2,217 (40%)	742 (13%)	1,353 (24%)	1,285 (23%)
Age (years)	63 (54,71)	63 (53,71)	62 (53,70)	62 (53,69)
Female	1,122 (51%)	375 (51%)	725 (54%)	660 (51%)
Hypertension	979 (44%)	298 (40%)	819 (61%)	576 (45%)
Diabetes mellitus	144 (7%)	101 (14%)	241 (18%)	243 (19%)
Heart rate (bpm)	62 (56,69)	62 (57,69)	62 (56,69)	63 (57,69)
Systolic BP (mmHg)	121 (109,137)	122 (109,138)	130 (116,144)	124 (111,140)
Diastolic BP (mmHg)	70 (63,77)	72 (65,79)	74 (68,81)	71 (65,78)
Body mass index (kg/m²)	27.2 (24.3,30.4)	23.7 (21.8,26.2)	29.4 (26.1,33.5)	28.6 (26.0,31.8)
Income				
< \$25k	348 (16%)	370 (50%)	387 (31%)	643 (51%)
\$25–50k	560 (26%)	162 (22%)	403 (32%)	401 (32%)
> \$50k	1,257 (58%)	207 (28%)	477 (38%)	210 (17%)
Glucose (mg/dL)	87 (81,95)	92 (86,101)	91 (83,102)	92 (84,105)
HOMA-IR	1.57 (1.13,2.34)	1.74 (1.32,2.52)	1.88 (1.23,2.82)	1.97 (1.39,3.10)
eGFR (ml/min/1.73m²)	75 (66,84)	81 (72,92)	85 (74,97)	82 (71,93)
Albuminuria	135 (6%)	92 (12%)	156 (12%)	158 (12%)
LDL cholesterol (mg/dL)	115 (95,136)	114 (96,132)	115 (94,136)	118 (98,139)
Triglycerides (mg/dL)	114 (77,164)	123 (87,172)	90 (66,122)	137 (97,196)
NT-proBNP (pg/ml) *	68 (34,136)	43 (17,90)	43 (17,94)	53 (23,107)
NT-proBNP < 5 pg/ml	67 (3%)	66 (9%)	137 (10%)	73 (6%)
LV mass index, (g/m²)	74 (65,85)	72 (65,81)	80 (71,92)	78 (69,90)
LV ejection fraction (%)	69 (64,74)	73 (68,76)	69 (63,74)	70 (64,74)

Data presented as number (percent) or median (25th, 75th percentiles). BMI = body mass index, BP = blood pressure, BPM = beats per minute, eGFR = estimated glomerular filtration rate, HOMA-IR = homeostatic model assessment of insulin resistance, LV = left ventricular, NT-proBNP = N-terminal pro B-type natriuretic peptide. Total N for LVMI and LVEF = 4,162.

* $P = 0.0001$ for differences in NT-proBNP by race/ethnicity. Total N for HOMA-IR = 4,831.

Multivariable-adjusted percent differences in N terminus-pro B type Natriuretic Peptide concentrations by race/ethnicity in the Multi-Ethnic Study of Atherosclerosis.

Table 2

Model	Covariates	White	Chinese	Black	Hispanic
1	Age, sex	Reference	-38% (-43%, -33%)	-36% (-40%, -32%)	-21% (-26%, -15%)
2	Anti-hypertensive med, diabetes mellitus heart rate, systolic BP, body mass index, eGFR, UACR, LDL cholesterol, triglycerides	Reference	-42% (-46%, -37%)	-42% (-46%, -37%)	-18% (-23%, -12%)
3	education, income	Reference	-46% (-50%, -41%)	-44% (-48%, -40%)	-25% (-30%, -19%)
4	LV ejection fraction, LV mass index	Reference	-41% (-46%, -35%)	-46% (-50%, -41%)	-27% (-33%, -20%)
5	HOMA-IR	Reference	-37% (-43%, -31%)	-45% (-49%, -39%)	-27% (-33%, -20%)

Data presented as percent differences in serum NT-proBNP levels (95% confidence interval). eGFR = estimated glomerular filtration rate; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low density lipoprotein cholesterol; LV = left ventricular BP = blood pressure; UACR = urine albumin to creatinine ratio.

Table 3

Proportion genetic ancestry according to self-reported race/ethnicity in the Multi-Ethnic Study of Atherosclerosis.

	<u>Self-reported race/ethnicity</u>			
	White	Chinese	Black	Hispanic
Genetic ancestry				
European	96.7% (94.7%, 97.9%)	1.7% (1.1%, 2.8%)	18.5% (10.6%, 30.5%)	50.0% (37.4%, 63.9%)
Chinese	0.6% (0.4%, 1.0%)	95.5% (93.7%, 97.0%)	0.8% (0.5%, 1.4%)	2.3% (1.0%, 5.8%)
African	1.6% (0.9%, 3.2%)	1.0% (0.6%, 1.6%)	79.1% (67.3%, 87.3%)	4.7% (1.8%, 14.8%)
Hispanic	0.4% (0.3%, 0.7%)	0.7% (0.4%, 1.5%)	0.6% (0.4%, 1.2%)	33.0% (12.2%, 47.7%)

Values are presented as median (25 ,75 percentiles).