American Journal of Preventive Cardiology 15 (2023) 100526

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Original Research

Racial and ethnic differences in circulating N-terminal pro-brain-type natriuretic peptide (NT-proBNP) in US adults

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ARTICLE INFO

Keywords:
Biomarkers
Race
Ethnicity
Epidemiology
Cardiovascular disease

ABSTRACT

Background: The presence and interpretation of racial and ethnic differences in circulating N-terminal pro-brain-type natriuretic peptide (NT-proBNP), a diagnostic biomarker for heart failure, are controversial.
Objective: To examine racial and ethnic differences in NT-proBNP levels among the general US adult population.
Methods: We performed a cross-sectional analysis of data from the 1999–2004 National Health and Nutrition Examination Survey (NHANES). We included 4717 non-Hispanic White, 1675 non-Hispanic Black, and 2148 Mexican American adults aged 20 years or older without a history of cardiovascular disease. We examined the associations of race and ethnicity with NT-proBNP using linear and logistic regression models in the overall population and in a younger, 'healthy' subsample.
Results: The mean age was 45 years. Median NT-proBNP levels were significantly lower among Black (29.3 pg/mL) and Mexican American adults (28.3.4 pg/mL) compared to White adults (49.1pg/mL, *P-values*<0.001). After adjusting for sociodemographic factors and cardiovascular risk factors, NT-proBNP was 34.4% lower (95%CI -39.2 to -29.3%) in Black adults and 22.8% lower (95%CI -29.4 to -15.5) in Mexican American adults compared to White adults. Our findings were consistent in a young, healthy subsample, suggesting non-cardiometabolic determinants of these differences.
Conclusions: NT-proBNP levels are significantly lower among Black and Mexican American adults compared with White adults, independent of cardiometabolic risk. Although race/ethnicity is a poor proxy for genetic differences, our findings may have clinical implications for the management of HF. However, studies in diverse populations are needed to characterize the biological basis of NT-proBNP variation.

1. Introduction

N-terminal pro-brain-type natriuretic peptide (NT-proBNP) is a stable amino acid fragment co-secreted with b-type natriuretic peptide from the ventricular cardiac myocytes in response to left ventricular strain or ischemia [1,2]. Unlike BNP, NT-proBNP is a biologically inert fragment of proBNP [3]. NT-proBNP acts in various ways to reduce cardiac overload, including salt homeostasis, vasodilation, natriuresis, and inhibition of the renin-angiotensin-aldosterone system [1,2]. NT-proBNP also supports the endocrine function of the heart by promoting fat metabolism and glucose handling [4]. NT-proBNP is routinely used in the staging and clinical management of heart failure.

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https://doi.org/10.1016/j.ajpc.2023.100526
Received 9 February 2023; Received in revised form 3 July 2023; Accepted 19 July 2023
Available online 20 July 2023

NT-proBNP is also associated with mortality and incident cardiovascular disease, especially heart failure, in community-based populations [5–7].

Prior studies have shown that people with obesity, even those with heart failure, have lower circulating NT-proBNP than those without obesity [8,9]. Compared to White people, Black people are more likely to have obesity [10], which is associated with lower natriuretic peptide levels. Black people are also more likely to develop heart failure than White people at earlier ages [11]. However, prior studies have speculated that there may be a genetic basis for the racial differences in NT-proBNP [12]. However, the underlying reasons for racial and ethnic differences in NT-proBNP levels are nonetheless incompletely understood.

While previous cohort studies have examined racial/ethnic differences in NT-proBNP, no previous study has examined race/ethnic differences in NT-proBNP in a nationally representative sample of US adults across the lifespan, and in a healthy subsample. We measured NT-proBNP in stored blood samples from participants in the National Health and Nutrition Examination Survey (NHANES) to understand its distribution and determinants in this nationally representative sample of the US population. The overarching objective of this study was to assess whether NT-proBNP differed according to race and ethnicity in the US adult population after accounting for traditional cardiovascular disease risk factors and sociodemographic differences.

2. Materials and methods

2.1. Data source

The NHANES is a cross-sectional, population-based survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention, designed to produce nationally representative estimates of the health status of the civilian, noninstitutionalized US population. NHANES uses a stratified, multistage probability sampling to select participants for in-home interviews and visits to a mobile examination center (MEC) for physical examinations and laboratory testing [13]. Since 1999–2000, NHANES has been conducted in 2-year cycles, and the present analysis pools data from the 1999–2000, 2001–2002, and 2003–2004 surveys. We obtained funding to measure NT-proBNP in surplus stored serum specimens from 1999 to 2004. NHANES was approved by the NCHS Institutional Review Board, and written informed consent was obtained from all participants. This stored serum study was approved by the ethics review board of the NCHS. Laboratory testing was completed between 2018 and 2020 at the University of Maryland School of Medicine (Baltimore, Maryland, USA).

2.2. Study population

We included US adults (age ≥20 years) in NHANES 1999–2004 who completed the in-home interview and MEC examination who were Non-Hispanic [NH] White, henceforth White, NH Black, henceforth Black or Mexican American ($N = 14{,}057$). We excluded participants who were pregnant ($N = 670$), with a self-reported history of cardiovascular disease ($N = 1621$), missing data on NT-proBNP ($N = 2242$), or missing covariates ($N = 984$). The final analytic sample included 8540 participants. A missing category was created for poverty-to-income ratio (missing $N = 537$) and drinking status (missing $N = 363$), which had greater than 4% missing values.

2.3. Measurement of NT-proBNP

NT-proBNP was measured in serum on the Roche e611 autoanalyzer. All measurements were performed from 2018-to 2020 at the University of Maryland School of Medicine in Baltimore, Maryland. The lower and upper limits of detection were (5 pg/mL, 35,000 pg/mL). The coefficient of variations (CV) were 3.1% (low, 46 pg/mL) and 2.7% (high, 32,805 pg/mL).

2.4. Other measures

Race and ethnicity were self-reported and categorized as White, Black, and Mexican American. BMI was calculated as weight in kilograms (kg) divided by height in meters-squared (m^2), and classified as normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2), or obese (≥ 30 kg/m^2) [14]. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or self-reported use of antihypertensive medications. Diabetes was defined as self-reported diagnosed diabetes, use of blood sugar-lowering medication, or a glycated hemoglobin ≥6.5%. High cholesterol was defined as ≥240 mg/dL or self-reported lipid-lowering medication. Cancer and was defined as self-reported cancer or malignancy. Respiratory disease was defined as self-reported emphysema and chronic bronchitis.

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2021) equation or albumin-to-creatinine ratio ≥30 mg/g [15]. Drinking status was defined as current moderate drinker (≤ 1 drink/day for female, ≤2 drink/day for male, current heavy drinker (drunk last year and over 12/life or drunk last year, former drinker (had at least 12 alcohol drinks/1 year and did not drink last year) and never drinker (never had at least 12 alcohol drinks/lifetime). Physical activity was defined as self-reported total physical activity level in MET-min/week and categorized as active (≥500 MET-min/week), somewhat active (500 MET-min/week) and inactive (no reported PA data.) Education was categorized as ≤high school education, some college, and ≥college graduate. Family income-to-poverty ratio was calculated as the ratio of a family's income to the appropriate poverty guidelines [16] and categorized as <130%, 130–349%, ≥350%, or missing. Employment status was categorized as employed or unemployed. Access to a routine place for healthcare was dichotomized from the question, "Is there a place that you usually go when you are sick or need advice about your health?" Health insurance status was dichotomized based on responses to the question, "Are you covered by health insurance or some other kind of healthcare plan?" Marital status was examined as a proxy of social support; individuals were categorized as married or cohabitating versus not. Birthplace was categorized as US-born or foreign-born.

2.5. Statistical analyses

All analyses were weighted and accounted for the complex sample survey design per NCHS guidelines. Participant characteristics, including means and percentages with corresponding standard errors, are presented by race/ethnicity. We examined the distributions of NT-proBNP levels by race and ethnicity using weighted kernel density plots. Low NT-proBNP was defined as the weighted 25th quartile of NT-proBNP (<22.27 pg/mL).

The associations of NT-proBNP (natural log-transformed) with race and ethnicity were evaluated using linear regression. Model 1 included age and sex. Model 2 included all variables in Model 1 plus socioeconomic status (including education, employment, usual source of healthcare, health visit in the past year, health insurance, income-to-poverty ratio, marital status, and birthplace). Model 3 included all variables in Model 2 plus cardiovascular risk factors and lifestyle factors (BMI, diabetes, hypertension, high cholesterol, CKD, cancer, respiratory disease, smoking status, drinking status, and physical activity). White adults (the largest group) were used as the reference group. The percent difference with 95% CI was calculated as: (eß-1) x100, where ß was the coefficient from linear regression models. We also used multivariable logistic regression to generate the adjusted odds ratios of low NT-proBNP by race and ethnicity. We constructed multiplicative interaction terms for race and ethnicity and potential factors associated with low NT-proBNP such as age, sex, BMI, diabetes, and hypertension diagnoses.

Examining the distribution of NT-proBNP in a young, healthy

population can help us evaluate differences that are unrelated to underlying disease or cardiovascular risk. Thus, we examined race and ethnic differences in the distribution of NT-proBNP in a healthy subsample defined as adults 20–39 years without diagnosed diabetes or CKD, with no hypertension diagnosis and no cholesterol lowering medication use, body mass index 18.5 to <25 kg/m^2, total cholesterol<200 mg/dL, and HbA1c<6.5%. We also examined racial and ethnic differences in the distribution of BMI, total cholesterol, systolic and diastolic BP to determine if a similar pattern would be observed. A p-value < 0.05 was considered statistically significant.

3. Results

There were 8540 participants aged 20 years or older whose data were weighted to the US adult population; 55.2% were White, 19.6% were Black, and 25.2% were Mexican American adults (Table 1). White adults were on average older than Black and Mexican American adults. Compared to White adults, Black and Mexican American adults were more likely to have indicators of low socioeconomic status including education and income. Black adults had the highest prevalence of obesity (40.1%), hypertension (35.6%), and CKD (12.0%). In a healthy subsample, differences in socioeconomic indicators were consistent with the larger sample (eTable 1).

Unadjusted median (p25, p75) NT-proBNP levels were significantly lower in Black adults (29.3 pg/mL, 13.8 - 61.5 pg/mL) as compared with White (49.1 pg/mL, 25.0 - 94.2 pg/mL) or Mexican American (28.3 pg/mL, 14.5 – 54.6 pg/mL) adults ($P<0.001$ for both comparisons). The prevalence of the low NT-proBNP (<22.27 pg/mL) was 39.9% among Black and 39.1% among Mexican American adults compared to 21.3% of White adults ($P<0.001$) (Table 1). The distribution of log NT-proBNP was shifted to the left in Black and Mexican American adults as compared to White adults in the overall population (Fig. 1, Panel A). When restricted to the healthy subsample, the shift in the distributions comparing White and Black adults was similarly pronounced (Fig. 1, Panel B). By contrast, there appeared to be no racial or ethnic differences in the distribution of BMI or total cholesterol in the healthy subsample (eFigure 1).

After adjusting for age and sex (Model 1), NT-proBNP was 30.8% lower (95%CI −36.2 to −25.5) in Black adults and 22.2% lower (95%CI −27.6 to −16.8) in Mexican American adults compared to White adults (Table 2). These differences remained after adjusting for sociodemographic factors (Model 2) and cardiovascular risk factors and lifestyle variables (Model 3) (Table 2). Compared to White adults, adjusted mean NT-proBNP was lower in Black adults (−17.2, 95%CI: −14.6, −19.9 pg/mL; $P<0.001$) and Mexican American adults (−11.4, 95% CI: −7.9, −14.9, pg/mL) (Table 2, Model 3) Compared to White adults, NT-proBNP was 34.4% lower among Black and 22.8% lower among Mexican American adults (Table 2, Model 3) In the multivariable logistic regression analyses examining interactions between race/ethnicity and potential factors associated with low NT-proBNP, only hypertension diagnosis was significant. ($p = 0.02$, eFigure 2)

In the young, healthy subsample, Black adults had lower NT-proBNP (adjusted mean difference 15.0, 95% CI: 8.6, 21.4 pg/mL; $P<0.001$) than White adults (Table 3, Model 3). However, there was no significant difference between Mexican American and White adults. (4.9, 95% CI: −7.0, 16.7 pg/mL; $p = 0.423$) (Table 3).

Table 1
Characteristics of US adults aged 20 and older according to race and ethnic group, NHANES 1999–2004, $N = 8540$.

	White	Black	Mexican American
Unweighted N	4717	1675	2148
Age, year	46.4 (0.3)	42.5 (0.4)	37.8 (0.6)
Male	48.0 (0.8)	45.3 (1.2)	55.1 (1.2)
Education			
≥College graduate	28.7 (1.9)	14.1 (1.1)	6.5 (0.9)
Some college	31.6 (0.9)	30.8 (1.3)	19.7 (1.6)
≤High school	39.8 (1.8)	55.2 (1.7)	73.8 (1.6)
Not employed	31.4 (0.9)	35.0 (1.5)	26.4 (1.5)
No usual source of healthcare	12.5 (0.7)	13.8 (1.1)	34.6 (2.0)
No health care visits in the past year	14.7 (0.8)	16.9 (1.1)	31.9 (1.4)
No health insurance	13.6 (0.9)	22.6 (1.5)	46.1 (2.4)
Poverty/income ratio			
350% +	48.4 (1.9)	24.4 (1.5)	16.5 (1.3)
130–350%	32.2 (1.2)	38.6 (1.4)	43.5 (1.4)
<130%	14.0 (1.5)	30.4 (1.8)	33.9 (2.2)
Missing	5.3 (0.6)	6.6 (0.7)	6.0 (1.0)
Not married/cohabitating	31.0 (0.9)	55.7 (1.7)	31.1 (1.5)
Not born in US	4.7 (0.7)	10.2 (2.2)	60.2 (3.1)
BMI, kg/m^2			
<25	36.2 (1.0)	28.6 (1.0)	29.6 (1.8)
25-<30	33.9 (0.7)	31.3 (1.3)	38.9 (1.0)
≥30	29.9 (0.9)	40.1 (1.3)	31.5 (1.4)
Diabetes	6.2 (0.4)	10.2 (0.6)	8.9 (0.7)
Hypertension	28.1 (1.0)	35.6 (1.2)	16.6 (1.7)
High cholesterol	25.4 (0.8)	17.7 (1.0)	15.3 (0.9)
Chronic kidney disease	9.6 (0.5)	12.0 (0.9)	10.3 (0.7)
Cancer or malignancy	9.3 (0.4)	3.5 (0.4)	1.6 (0.3)
Respiratory disease	7.7 (0.5)	5.8 (0.7)	2.7 (0.3)
Smoking status			
Never	48.9 (1.3)	58.9 (1.9)	57.5 (1.2)
Former	26.2 (1.0)	14.5 (1.1)	20.1 (0.9)
Current	25.0 (1.0)	26.6 (1.5)	22.4 (1.2)
Drinking status			
Current moderate drinker	35.7 (1.6)	29.2 (1.1)	22.7 (1.5)
Current heavy drinker	35.6 (1.2)	29.1 (1.4)	45.3 (1.4)
Former drinker	15.0 (1.0)	16.8 (1.0)	14.0 (0.9)
Never drinker	10.1 (1.5)	18.8 (1.5)	11.7 (0.8)
Missing	3.5 (0.4)	6.1 (0.6)	6.3 (0.7)
Total physical activity level, MET-min/week			
Inactive, no reported PA data	11.2 (0.8)	24.9 (1.4)	26.1 (1.8)
Somewhat active, <500 MET-min/week	19.5 (0.8)	21.7 (1.1)	22.4 (1.4)
Active, ≥500 MET-min/week	69.3 (1.1)	53.4 (1.6)	51.5 (2.0)
*Median NT-proBNP pg/mL	49.1 (25.0–94.2)	29.3 (13.8–61.5)	28.3 (14.5–54.6)
Quartiles of NT-proBNP			
<22.27 pg/mL (25th percentile)	21.3 (0.8)	39.9 (1.7)	39.1 (1.8)
<44.46 pg/mL (50th percentile)	46.0 (0.8)	65.0 (1.5)	67.4 (1.7)
<86.96 pg/mL (75th percentile)	72.5 (0.8)	83.1 (1.2)	87.6 (1.1)
<824.9 pg/mL (99th percentile)	98.9 (0.1)	99.0 (0.2)	99.6 (0.1)
NT-proBNP ≥125 pg/mL	17.0 (0.6)	11.2 (0.8)	6.3 (0.8)

Abbreviations: NT-proBNP: N-terminal pro-B-type natriuretic peptide, MET: metabolic equivalent, BMI: Body Mass Index.
*Median (p25, p75).

4. Discussion

We sought to examine whether there were racial and ethnic differences in NT-proBNP in a nationally representative sample of US adults that were independent of other demographic characteristics and cardiovascular risk factors. Our main finding was that Black and Mexican American adults had significantly lower plasma NT-proBNP than White adults (33.4% Black, 20.5% Mexican American) after accounting for potential confounders, both overall and in a young, healthy subsample. The racial and ethnic difference in NT-proBNP persisted across age groups, sex, BMI categories, and diabetes and hypertension status.

Prior community-based cohort studies [17–19] have examined racial and ethnic differences in NT-proBNP. These studies have consistently observed 27% to 44% lower NT-proBNP in Black adults than White adults, with no ethnic differences between non-Hispanic White and Hispanic adults [17–19]. Our results confirm and extend previous findings in the US adult population. We demonstrated that the

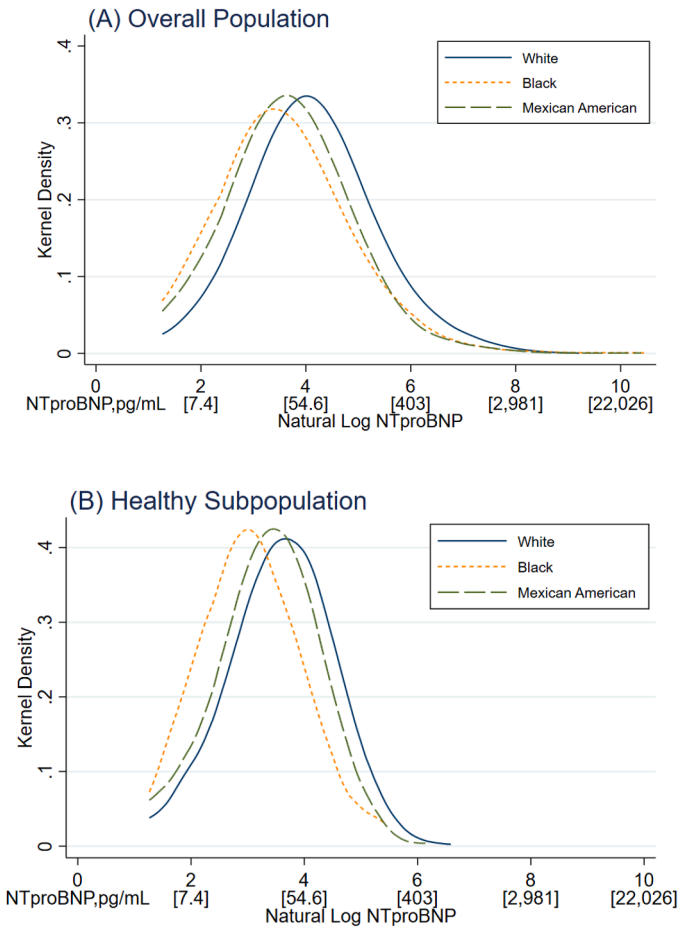

Fig. 1. Distribution of NT-proBNP according to race/ethnic groups, US adults aged 20+ (Panel A) and the healthy subsample (Panel B), NHANES 1999–2004. *Healthy defined as 20–39 years without diagnosed diabetes or CKD, with no hypertension and no cholesterol lowering medication use, body mass index 18.5 to <25 kg/m2, total cholesterol<200 mg/dL and HbA1c<6.5%.

race/ethnic differences in NT-proBNP persisted after accounting for factors that previously have been shown to influence NT-proBNP levels, such as obesity and diabetes [20,21]. The lower levels of NT-proBNP in Black compared to White adults were evident in a "healthy" subsample with no cardiovascular risk factors, suggesting that the observed disparities are independent of underlying cardiovascular risk.

Systematic race/ethnic differences that appear in young, healthy adults and are independent of risk factors for disease may hint at underlying genetic determinants that differ by ancestry. We make this statement with caution. Nonetheless, a similar debate has arisen regarding small but systematic glucose-independent "racial differences" in HbA1c and hemoglobin, which are almost certainly explained by genetic variation that differs by ancestry [22–24]. Genetic ancestry may be a potential explanation for the observed racial and ethnic differences in NT-proBNP. In the ARIC [17] and Multi-ethnic Study of Atherosclerosis (MESA) [18] cohorts, European ancestry was associated with higher NT-proBNP levels among Black adults. Black people and Hispanic people have the highest levels of genetic admixture, while White and Asian adults have the least amount of genetic admixture [18,25].

Although prior studies have suggested that low NT-proBNP is heritable [26], genetic differences in the natriuretic peptide system are incompletely understood [27,28]. Among ARIC participants, there was no racial difference in the frequency of rs198389, a variant in the Natriuretic Peptide Precursor Gene B (NPPB) gene, which is responsible for transcription, translation, and/or post-translational processing of natriuretic peptides [29]. However, Black people in the Dallas Heart Study, MESA, and ARIC studies had a higher prevalence (10–13%) of a genetic variant in *Corin*, an enzyme responsible for the processing of NP, and linked with a higher risk of hypertension [28]. Thus, the lower-than-expected NT-proBNP levels in Black people may suggest impaired processing and higher clearance of the circulating NPs [30]. Among 2790 Black adults in the Jackson Heart Study, single nucleotide polymorphisms (SNPs) were identified in the NPPB (rs198389, minor allele frequency=0.40, $P = 1.18 \times 10^{-09}$; rs12406089, minor allele frequency=0.39, $P = 3.67 \times 10^{-09}$; and rs6668659, minor allele frequency=0.37, $P = 3.08 \times 10^{-09}$), and Kallikrein plasma factor (KLKB1) genes. While these variants were both associated with hypertension and BP control [31], these do not seem to be associated with lower natriuretic peptide.

It is important to understand the clinical implications of any biological determinants of NT-proBNP because NT-proBNP is a diagnostic biomarker for heart failure, a condition that affects over 6 million US adults [32]. It is projected that the burden of heart failure will continue to increase, with more than 8 million US adults living with heart failure by 2030 [32]. Racial disparities in heart failure are also well--documented—Black adults have higher rates of heart failure and develop heart failure at younger ages [32–34]. Moreover, the population burden of pre-clinical heart failure (Stages A and B) is three to four times higher than clinical heart failure [35,36]. Higher NT-proBNP is predictive of progression for Stage B but not Stage A in a community-based population [37].

In our analysis, we observed significant differences in NT-proBNP between White adults and Mexican American adults. An analysis of NT-proBNP in the Dallas Heart Study which sought to examine racial/ethnic differences in NT-proBNP among 3148 adults (51% Black, 31% White, 18% Hispanic[*specific ethnicity unknown*]) did not find differences in NT-pro-BNP between White and Hispanic participants [19]. However, our results are consistent with those from the MESA Study [18] and

Table 2
Adjusted absolute and percent differences (95% CI) in NT-proBNP (pg/mL) according to Race/Ethnicity, US adults aged 20+, NHANES 1999–2004 ($N = 8540$).

	White	Black	Mexican American	Black vs. White	Mexican American vs. White	Black vs. White	Mexican American vs. White
	Mean NT-proBNP, pg/mL			Absolute difference (95% CI), pg/mL	Absolute difference (95% CI), pg/mL	% difference (95% CI)	% difference (95% CI)
Crude	49.2	30.7	27.8	−18.5 (−15.4, −21.6)	−21.4 (−18.6, −24.2)	−37.6 (−43.3, −31.9)	−43.6 (−48.6, −38.6)
Model 1	37.5	25.9	29.2	−11.6 (−9.4, −13.7)	−8.3 (−6.2, −10.4)	−30.8 (−36.2, −25.5)	−22.2 (−27.6, −16.8)
Model 2	50.5	33.1	38.6	−17.4 (−14.6, −20.2)	−11.8 (−8.4, −15.2)	−34.5 (−39.5, −29.4)	−23.4 (−29.9, −16.9)
Model 3	50.1	32.8	38.6	−17.2 (−14.6, −19.9)	−11.4 (−7.9, −14.9)	−34.4 (−39.3, −29.6)	−22.8 (−29.6, −16.1)

Model 1: age and sex.
Model 2: variables in Model 1 + education, employment, usual source of healthcare, health visit in the past year, health insurance, PIR, marital status and birthplace.
Model 3: model 2 + BMI, diabetes, hypertension, high cholesterol, CKD, cancer, respiratory disease, smoking status, drinking status and physical activity.

Table 3
Adjusted absolute and percent differences (95% CI) in NT-proBNP (pg/mL) according to Race/Ethnicity, Healthy* subsample of US adults aged 20+, NHANES 1999–2004 ($N = 720$).

	White	Black	Mexican American	Black vs. White	Mexican American vs. White	Black vs. White	Mexican American vs. White
	Mean NT-proBNP, pg/mL			Absolute difference (95% CI), pg/mL	Absolute difference (95% CI), pg/mL	% difference (95% CI)	% difference (95% CI)
Crude	35.8	21.8	27.3	−13.9 (9.6, 18.2)	−8.5 (3.4, 13.5)	−38.9 (−49.4, −28.5)	−23.7 (−36.6, −10.8)
Model 1	40.0	26.9	32.7	−13.1 (9.8, 16.5)	−7.4 (0.9, 13.8)	−32.7 (−40.5, −25.0)	−18.4 (−34.0, −2.9)
Model 2	45.6	31.0	39.7	−14.6 (9.9, 19.3)	−5.9 (−4.8, 16.6)	−32.0 (−38.8, −25.2)	−12.9 (−35.4, 9.6)
Model 3	47.8	32.7	42.9	−15.0 (8.6, 21.4)	−4.9 (−7.0, 16.7)	−31.4 (−39.6, −23.2)	−10.2 (−33.7, 13.3)

Model 1: age and sex adjusted.
Model 2: model 1 + education, employment, usual source of healthcare, health visit in the past year, health insurance, PIR, marital status and birthplace.
Model 3: model 2 + hypertension, cancer, respiratory disease, smoking status, drinking status and physical activity.
* Healthy adults defined as 20–39 years without diagnosed diabetes or CKD, with no hypertension and no cholesterol lowering medication use, body mass index 18.5 to <25 kg/m2, total cholesterol<200 mg/dL and HbA1c<6.5%.

Diabetes Prevention Program [38] where Hispanic participants had significantly lower NT-pro-BNP than White participants. We focused on Mexican American adults, one of the largest Hispanic groups in the US. The rationale for excluding "Other Hispanic Americans with unspecified Hispanic ethnicity" was to reduce heterogeneity in genetic ancestry and more clearly observe race/ethnic differences. Our approach is consistent with prior calls to disaggregate data on Hispanic subgroups, which may mask the heterogeneity in CVD risk factors and genetic ancestry [39,40].

Our findings come at a time when there is a greater acknowledgement that race/ethnicity is not a biological construct but a social one [41,42]. The consideration of race in clinical algorithms may further exacerbate health disparities and thwart equal treatment of racial/ethnic minority groups [42]. Recently, race has been removed in the calculation of eGFR [18]. Prior studies have called for "race-specific" cut-points for NT-proBNP [43,44]. However, Parcha et al. [45] have shown that although Black adults had 21% lower NT-proBNP than White adults in the Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in HF(GUIDE-IT) trial, NT-proBNP concentrations of ≤1000 pg/mL were equally prognostic in guiding heart failure management in Black and White participants.

We think any calls for race-specific cut-points for NT-proBNP may be premature without a full understanding of the underlying biological factors that are driving differences in NT-proBNP by race and ethnicity. Since genetic variants that affect NT-proBNP affect only a minority of Black adults, thus using race as a proxy for such variants could result in substantial misclassification. In the absence of an understanding of the full genetic determinants of NT-proBNP, race-specific cut points are likely to result in miscategorization of risk and could result in harm and potentially perpetuate racial disparities.

Our study is the first in a nationally representative sample of community-dwelling NH Black, Mexican American, and NH White adults in the US of all ages who were free of cardiovascular disease. Major strengths of our study were the nationally representative sample, broad age range, detailed information on demographic and cardiovascular risk factors measured in a standardized fashion by trained personnel, and ability to rigorously examine the distributions of NT-proBNP in a young, healthy subsample.

5. Study limitations

There are several limitations are important to consider in interpreting our results. First, despite adjustment for confounding clinical and sociodemographic factors, the potential for residual confounding cannot be ruled out. Second, cardiovascular disease was self-reported and may be subject to misclassification. Third, we did not measure left ventricular mass, which is a key determinant of NT-proBNP levels. Fourth, participants self-reported their race and ethnicity, and we did not have information on genetic ancestry. Although the NHANES 1999–2004 samples included Mexican Americans, they are not representative of all Hispanic ethnic subgroups in the US. Furthermore, Asian Americans were not oversampled in NHANES until later waves (2011–2018), which prevents an examination of NT-proBNP levels among Asian Americans in this analysis.

6. Conclusions

We demonstrated systematic differences by race/ethnicity in the distribution of NT-proBNP in a nationally representative adult population and in a subsample of young, healthy adults. Recent calls for race-specific cut-points in NT-proBNP may be premature in the absence of a clear understanding of the drivers of these differences. Additional studies of the biological basis of NT-proBNP variation in racially homogenous populations of diverse genetic ancestry are needed to help us understand the clinical relevance of these findings. Further studies to understand the clinical implications of racial and ethnic differences in NT-proBNP are warranted.

CRediT authorship contribution statement

Yvonne Commodore-Mensah: Conceptualization, Writing-Original draft preparation, **Dan Wang:** Data curation, Software, Visualation, Formal analysis . **Yein Jeon:** Data curation, Software, Visualation, Formal analysis. **Kathryn Foti:** Writing-Original draft preparation. **John William McEvoy:** Writing- Reviewing and Editing. **Josef Coresh:** Writing- Reviewing and Editing, Funding Acquisition. **Olive Tang:** Writing- Reviewing and Editing. **Justin B. Echouffo-Tcheugui:** Writing- Reviewing and Editing, **Robert Christenson:** Investigation, Methodology, Funding Acquision. **Chiadi Ndumele:** Writing- Reviewing and Editing. **Elizabeth Selvin:** Conceptualization, Investigation, Methodology, Funding Acquision, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding support and disclosures

This work was funded by a grant from the Foundation for the National Institutes of Health Biomarkers Consortium to the Johns Hopkins Bloomberg School of Public Health (PI: Elizabeth Selvin). The

Foundation for the National Institutes of Health received support for this project from Abbott Laboratories, AstraZeneca, Johnson & Johnson, the National Dairy Council, Ortho Clinical Diagnostics, Roche Diagnostics, and Siemens Healthcare Diagnostics. Dr. Selvin was also supported by NIH/NHLBI grant K24 HL152440.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100526.

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