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Socioeconomic Status, HBB, and TTR Variants, and Cardiorenal Outcomes: The Regards Study

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SOCIOECONOMIC STATUS, HBB, AND TTR VARIANTS, AND CARDIORENAL OUTCOMES: THE REGARDS STUDY

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EPIDEMIOLOGY

ABSTRACT

Blacks are disproportionately affected by heart failure (HF) and end-stage renal disease (ESRD). While poorer health outcomes in Blacks have been associated with social determinants of health, there are some biological differences worth noting, namely genetic risk variants for both *TTR* and *HBB*. These genetic risk variants are known to confer additional risk in the development of heart failure and end-stage renal disease, respectively. While we understand these genetic variants aren't fully penetrant, and genetics and are not deterministic, we aimed to examine additional factors and mechanisms responsible for the increased risk in HF and ESRD in Blacks. Neighborhood socioeconomic status (nSES) is an environmental exposure known to confer an additional mortality risk beyond individual socioeconomic status. Our primary research objective was to determine the role nSES as a modifier of the association between TTR and HBB genetic variants and their respective cardiorenal outcomes. To test the association between the genetic risk variants and the incident outcomes we used a multivariable Cox proportional hazards regression. We identified and adjusted for potential confounders and while there was insufficient evidence to support our hypothesis, our study suggests that worse cardiorenal risk factors of people in lower nSES neighborhoods may be more indicative in the association between genetic risk variants and cardiorenal outcomes.

Keywords: End-Stage Renal Disease (ESRD), Heart Failure (HF), TTR, HBB, Cardiorenal, Neighborhood Socioeconomic Status (nSES)

DEDICATION

This project is dedicated to my parents Robert and Tammi Abrams, my siblings Robert and Kiera, and my beautiful nieces and nephew Kailyn, Amelliya, and Jalen. You all have been a constant source of support and encouragement during the challenges of graduate school and life. I would also like to dedicate this thesis work to my many friends but especially to Clinton, who has constantly reminded me that I could handle anything I was thrown. I am stronger because of you. And, to Joel, Sam, and Ashley who have been with me since the very beginning of my graduate school journey, you all have been my biggest cheerleaders and I am so thankful to have met each one of you. To all my friends and family, no words can truly express my gratitude for your words of encouragement and the support you've offered me. **WE DID IT**!

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INTRODUCTION

Chronic disease affects nearly 60% of the US population [1]. However, the disease burden is not shared equally. Heart failure, and renal disease remain leading causes of death for Black Americans compared to individuals of any other racial/ethnic backgrounds [1-3]. Recent mortality data reveal that age-adjusted rates for heart failure (HF) in the Black population is significantly higher (91.5 deaths per 100,000) than in Whites and Hispanics (87.3, 53.3 per 100,000, respectively) despite the overall decline in HF mortality trends [1]. Blacks are also at a 3.5 times higher risk for progression from early stage CKD to end-stage renal disease (ESRD) compared to Whites [4]. While poorer health outcomes in Black Americans have been associated with social determinants of health, there are some biological differences noted.

Hemoglobin subunit beta (HBB), and Transthyretin (TTR) gene variants are strongly associated with cardio-renal traits that overburden the Black population. Specifically, variant forms of HBB that cause sickle cell disease, have been associated with a two-fold increased risk of incident ESRD, in those that carry the sickle cell trait (SCT) as opposed to non SCT carriers [5, 6]. Variants of TTR have also been shown to have a significant association with heart failure (HF) [7]. The most common type variant (TTR V122I) of the TTR gene is carried by nearly 4% of Black Americans [8] and can confer a two-fold increased risk of heart failure [9].

Whereas we know the genetic variants associated with these cardiorenal traits are not fully penetrant, and genetics are not deterministic, we aim to examine additional factors and mechanisms responsible for increased risk for ESRD and HF in Blacks.

The effects of socioeconomic status (SES) in adults are well documented. Studies in the U.S. have shown that lower SES corresponds to worse health outcomes, while higher SES was associated with not only better health outcomes but a decrease in chronic disease prevalence, more specifically heart failure, chronic kidney diseases, and end-stage renal disease [10]. Neighborhood socioeconomic status (nSES) is an environmental exposure known to confer independent risk for individual health outcomes, and a strong contributor of adverse cardiorenal health outcomes, even after accounting for potential individual-level confounding factors [11, 12]. In the REGARDS study, it was found that residence in disadvantaged neighborhoods was associated with a higher risk of HF, particularly among those without diabetes mellitus (DM) [13]. Additionally, when examining interactions between nSES and individual SES; lower nSES were still associated with poorer health outcomes in those with lower individual SES outcomes [14].

While the association between nSES and poorer health outcomes does exist, research suggests the relationship is not casual but rather fundamental in determining social inequalities that influence health and one's ability to move to neighborhoods of higher SES [15]. Given these findings, our primary research objective is to determine the role of nSES as a modifier of the associations between genetic variants found within HBB, TTR and respective cardiorenal outcomes (ESRD and HF).

METHODS

Study Design

The REGARDS study is a national population-based longitudinal study of 30,239 non-Hispanic Blacks and White adults ages 45 years and older [16]. The aims of this study are to investigate stroke epidemiology in the United States and investigate factors that contribute to the excess stroke mortality among at-risk populations. The study oversampled individuals from the stroke belt region (North Carolina, South Carolina, Tennessee, Alabama, Georgia, Mississippi, Louisiana, and Arkansas). This study is described in detail elsewhere [16]. Our study examines incident heart failure and incident end-stage renal disease amongst African Americans.

Study Population

For the current study, we only included non-Hispanic Blacks that had genetic information available for both HBB (rs344) and TTR (rs76992529) risks variants (N=7,958 for TTR; N=7,879 for HBB). We excluded any individuals with missing information on the genetic variants, their prospective outcomes, age, sex, principal components of ancestry, neighborhood socioeconomic status (nSES), diabetes, hypertension, smoking, physical activity, as well as alcohol. Those with prevalent ESRD and HF were also excluded resulting in a final sample. Data for demographics, medical history, and health behaviors were collected during a phone interview. During the in-home exam, blood pressure, weight, height, electrocardiogram blood, and urine samples

were collected [16]. Any additional follow-up consisted of collecting information regarding hospitalizations, ER visits, and/or deaths. All participants provided informed consent, and the REGARDS study was approved by the IRB of the participating centers.

Genotypic Assessment

All self-reported non-Hispanic Black participants who consented to genetic research were genotyped for TTR risk variants (rs76992529) using the Infinium MEGA-EX array from Illumina (San Diego, CA, USA) [17]. Consenting participants were also genotyped for sickle cell trait (SCT), this was done using TaqMan SNP Genotyping Assays and is fully detailed in previous study [5, 6]. Quality control measures were performed at both the sample and variant level. Principal components of ancestry were created from the GWAS data using EIGENSTRAT software, and those considered outliers were excluded from further analysis [18].

Study Outcomes

Incident Heart Failure

Incident heart failure was previously defined in another REGARDS study as an incident heart failure hospitalization or death due to heart failure based on an adjudication of medical records by trained physicians [19] . This information was collected through follow-up telephone interview with participants every 6 months. Adjudication of heart failure events were based on signs and symptoms, laboratory studies, electrocardiograms, chest x-ray, and assessments of left ventricular function. Signs and symptoms of HF included paroxysmal nocturnal dyspnea, orthopnea, abnormal jugular vein distension,

pulmonary rales, cardiomegaly, central venous pressure >16 mm Hg, edema, nocturnal cough, exertional dyspnea, hepatomegaly, pleural effusion, heart rate >120/minute, and ≥4.5-kilogram weight loss in 5 days with diuresis. A binary variable was designed to exclude individuals with possible heart failure at baseline based on the following: (1) those with digoxin use and no atrial fibrillation, (2) carvedilol use, (3) spironolactone use, (4) hydralazine + isosorbide mono- or dinitrate use, (5) loop diuretic (furosemide, bumetanide, torsemide) use, or (6) (ACE/ARB) + beta blocker uses and no hypertension [19].

Incident End Stage Renal Disease

Incident ESRD, was previously defined by linkage of the cohort to USRDS through 2013 [6, 20]. A binary variable was designed based on the eGFR <15, self-reported use of dialysis, and/or having the 1st USRDS service after the baseline in-home visit, among those who did not have ESRD at baseline. This information was collected through telephone interview, self-administered questionnaire, and in-home examination.

Covariates of Interests

Age, sex, current smoking status (yes, no), alcohol use (current, never, past), and physical activity (1 to 3 times per week, 4 or more times a week, none), were all self-reported measures collected at baseline via telephone interview. Hypertension was determined through a baseline systolic blood pressure ≥140 or a diastolic blood pressure ≥90 or self-reported use of anti-hypertension medication. Diabetes was defined through fasting glucose levels ≥126, non-fasting glucose ≤200, or use of diabetes medication.

Neighborhood socioeconomic status (nSES) as previously used in REGARDS was defined as a composite z-score based on 6 census tract variables: (1) log of median household income, (2) log of median value of owner-occupied housing units, (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 using the neighborhood deprivation index from the 2000 census, created from census-tract-based baseline address [20, 21]. This nSES variable was recoded into quartiles and categorized ordinally. Principal components of ancestry were included in each of the models [18].

Statistical Analyses

Descriptive statistics by genetic risk variants were calculated using frequencies for our categorical data and continuous data was summarized using means, and standard deviations. To test the association between the genetic risk variants and the incident outcomes we used a multivariable Cox proportional hazards regression. We adjusted for confounders in the following manner: Model 1 was our base model which included the risk genotype association with the outcome adjusting for age, sex, principal components of ancestry; Model 2 additionally included the neighborhood deprivation variable; Model 3 we added both diabetes and hypertension; Model 4 we added smoking, physical activity, and alcohol use. For Model 5 we added the interaction between risk genotype and nSES. All analyses were performed using SAS 9.4 and all statistical tests were conducted at a α=0.05 significance level.

RESULTS

TTR Baseline Characteristics

Baseline characteristics were summarized by TTR risk variant status and reported in **Table 1a**. Among 6,967 Black non-Hispanic participants from the REGARDS incident heart failure cohort, 3.2% (n=220) carried the TTR gene variant (rs76992529). The mean age of subjects with the TTR risk variant was 62, ranging from 42 to 86. Of the group of individuals, that carried the genetic risk variant of interest, and about 61.4% were females. 21.8% (n=48) were smokers, 45.5% (n=100) were current drinkers and 46.4% (n=102) reported being physically active 1 to 3 times per week. 24.6% were classified as having diabetes and 65.9% with hypertension. The TTR non-risk group was overall similar except the they seemed to be more physically active, where 27.5% reported being physically active 4 or more times per week (vs. 21.4% in the TTR group) and had slightly poorer neighborhood deprivation index mean of -3.3 (vs. -3.0 mean neighborhood deprivation index of the TTR group).

HBB Baseline Characteristics

Baseline characteristics were summarized by HBB risk variant status and reported in **Table 1b**. Among the 7,879 Black non-Hispanic participants from the REGARDS

incident end stage cohort, 7.5% (n=590) carried the HBB risk variant (rs344). The average age of individuals with the HBB risk variant was 63, ranging from 45 to 93 and of that same group that carried the HBB risk variant of interest 64.6% (n=381) were female. 19.3% (n=114) were smokers, 40.9% (n=241) were current drinkers and 37.1% (n=219) reported being physically active 1 to 3 times per week. 30.7% had diabetes and 69.2% had hypertension. The groups were overall similar except there were more individuals in the HBB group who reported never drinking (37.1% vs. 33.5% of those without the HBB variants who reported never drinking).

Association of nSES and TTR gene risk variant with Incident Heart Failure in Blacks

Overall, there were a total of 6,967 individuals in the heart failure cohort, of that number 380 (5.5%) experienced an incident heart failure event. Of the incident heart failure cohort, 24 (6.3%) of participants carried the TTR gene variant of interest. In the base model, after adjusting for age, sex, and principal components of ancestry, TTR was associated with a two-fold higher risk of heart failure (HR: 2.186; 95% CI:1.443-3.310), as shown in **Table 2**. In Model 2, where nSES was added to the base model, nSES was associated with a 18.8% increased risk of heart failure (HR: 1.1878; 95% CI: 1.083-1.301) for every 1 increase in quartiles. In Model 3, diabetes and hypertension were added to the previous model and both TTR and nSES had similar associations; where in Model 3 TTR was associated with a 2.3 times higher risk (HR: 2.337; 95% CI:1.542-3.543) and nSES was associated with a 16.7% increased risk (HR: 1.167; 95% CI:1.065-1.280) of heart failure. In Model 4, smoking, physical activity, and alcohol use were added to the previous model the hazard ratio for TTR remained consistent with those in Model 3 (HR: 2.310; 95% CI:1.523-3.503) while nSES still was associated with a 13.6%

(HR: 1.136; 95% CI:1.035-1.247) increased risk for heart failure. There was no interaction between nSES and TTR gene variant on the risk of incident heart failure (p-value: 0.5765).

Association of nSES and HBB gene risk variant with Incident Heart Failure in Blacks

Overall, there were a total of 364 incident cases of end-stage renal disease during follow-up with 44 (12.1%) of those individuals with the HBB gene variant of interest. As shown in **Table 2**. Model 1, HBB was associated with a 76.8% (HR: 1.768; 95% CI: 1.288-2.243) increased risk for ESRD after adjusting for age, sex, and 10 principal components of ancestry. In Model 2, nSES was added to the base model and was associated with an increased risk of 19.1% (HR: 1.191; 95% CI: 1.085-1.307) for every one quartile change. HBB was associated with a 78.7% (HR: 1.787; 95% CI: 1.302-2.454) increased risk of ESRD. After controlling for diabetes and hypertension in Model 3, the associated risk between HBB and incident ESRD remain consistent (HR: 1.787; 95% CI: 1.301-2.455), and the associated risk for nSES was 13.5% (HR: 1.135; 95% CI: 1.034-1.246). In Model 4, smoking, physical activity, and alcohol use were added to Model 3, and HBB was associated with a 90% (HR: 1.901; 95% CI: 1.383-2.614) increased in risk while nSES was associated with a 10% (HR: 1.101; 95% CI: 1.002-1.210) increased risk in ESRD. There was no interaction between nSES and HBB gene variant on the risk of end-stage renal disease (p-value: 0.121).

DISCUSSION

Blacks are disproportionately affected by cardiorenal diseases and while social determinants of health, are indicators for poorer health outcomes biological differences are also indicative of these outcomes [1-4]. Using the large REGARDS cohort study, it's been previously reported that both HBB and TTR are positively associated with higher risks for both incident heart failure and incident ESRD [6, 8, 22]. The study has also previously reported on a positive association between nSES and HF [14, 21, 23, 24]. Here we took these studies further and evaluated whether nSES could modify known associations between these African Ancestry risk variants and cardiorenal outcomes.

Although there is not much research surrounding the associations between nSES and incident ESRD, our findings were consistent with other studies have that looked at nSES modifying the association between Black race and poorer health outcomes [20, 25]. Previous studies that investigated neighborhood socioeconomic status as a modifier to mortality risk indicated that nSES was a stronger independent correlate of mortality over genetic ancestry [12]; as well as, low SES neighborhood conferring additional mortality risk beyond individual SES [11]. However, when examining the statistical interactions of both TTR and HBB, independently with nSES, we didn't see any evidence of neighborhood socioeconomic status modifying the known association between these

genetic variants and their respective outcomes. The associations were weakened between both TTR/HBB risk variants and their respective cardiorenal outcomes after further adjustment for these cardiorenal risk factors. Since nSES can contribute to the development of cardiorenal risk factors through things such as: access to care, exposure to environmental factors such as racial discrimination, high levels of unemployment, availability to health foods, or schooling, as well as social norms. Thus, people living in those low nSES neighborhoods have a higher level of unhealthy behaviors such as smoking, poor diet, and physical inactivity and, therefore, a higher prevalence of cardiorenal risk factors like diabetes and hypertension. Which requires a further look into our nSES variable and if this measure is one that truly captures our population of interest.

Further examination into these inconsistencies revealed that a possible reasoning behind our findings is that more well-off Black families end up living in poorer areas than White families with similar or even lower incomes [26, 27]. Since our cohorts consists of only Black Americans, this could potentially explain why we were not able to see any evidence that suggest that nSES modifies the known associations since research suggest that neighborhood deprivation is not causing poorer health but rather reflect more fundamental social inequalities present at the individual socioeconomic level [28]. However, we understand the overall difficulty of separating individual SES from nSES.

Our study is not without limitations. For the incident heart failure cohort, 6.3% of the observed heart failure population carried the gene of interest. As well as the ESRD cohort, where 7.5% of the population carried the gene variant of interest, and 364 total events were observed. Despite having a relatively large sample size, our interaction effects would have needed to be very large for us to observe with the low TTR/HBB risk

variants frequency and small event rate. Additionally, despite the inclusion of a variety of confounding variables, there still may be some residual confounding in our models. The strengths of our study include the use of a large population-based sample of Black Americans with data on comorbidities for both heart failure and end-stage renal disease.

CONCLUSION

In conclusion, in a large, population-based study of Black adults, both TTR and HBB risk variant are important predictors of an increased risk of heart failure and end-stage renal disease, respectively. While there was insufficient evidence to support our hypothesis, this research does present an opportunity to further explore other social inequalities and how they may modify the relationship between nSES and poorer health outcomes. We also plan to explore how individual SES may modify the known relationship between these genetic risk variants and their associated cardiorenal outcomes.

Table 1a. Baseline Characteristics of Incident Heart Failure Cohort by TTR Risk Variants

Variables	TTR (Yes) (N=220)	TTR (No) (N=6747)
Age, years	62.57 (42.0, 86.0)	63.36 (45.0, 96.0)
Female	135 (61.4%)	4089 (60.6%)
Current Smokers	48 (21.8%)	1259 (18.7%)
Alcohol Use		
Current	100 (45.5%)	3000 (44.5%)
Never	78 (35.5%)	2221 (33.0%)
Past	42 (19.1%)	1526 (22.6%)
Physical Activity		
1 to 3 times per week	102 (46.4%)	2555 (37.9%)
4 or more per week	47 (21.4%)	1853 (27.5%)
None	71 (32.3%)	2339 (34.7%)
Diabetes	54 (24.6%)	1768 (26.2%)
Hypertension	145 (65.9%)	4680 (69.4%)
Neighborhood Socioeconomic Status*	-3.0 (-11.6, 13.3)	-3.3 (-13.8, 14.3)

*Neighborhood Deprivation Index

Table 1b. Baseline Characteristics of Incident ESRD Cohort by HBB Risk Variants

Variables	SCT (Yes) (N=590)	SCT (No) (N=7289)
Age, years	63.0 (45.0 93.0)	63.72 (45.0, 94.0)
Female	381 (64.6%)	4418 (60.6%)
Current Smokers	114 (19.3%)	1309 (18.0%)
Alcohol Use		
Current	241 (40.9%)	3105 (42.6%)
Never	219 (37.1%)	2441 (33.5%)
Past	130 (22.0%)	1743 (23.9%)
Physical Activity		
1 to 3 times per week	219 (37.1%)	2708 (37.2%)
4 or more per week	162 (27.5%)	1905 (26.1%)
None	209 (35.4%)	2676 (36.7%)
Diabetes	181 (30.7%)	2146 (29.4%)
Hypertension	408 (69.2%)	5228 (71.7%)
Neighborhood Socioeconomic Status*	-3.5 (-11.9, 11.1)	-3.4 (-14.4, 14.3)

*Neighborhood Deprivation Index

Table 2. Association between genetic risk variants and respective cardiorenal outcomes

	Model 1		Model 2		Model 3		Model 4		Model 5 Interaction Term
	HR 95% CI	p-value	HR 95% CI	p-value	HR 95% CI	p-value	HR 95% CI	p-value	p-value
TTR	2.186 (1.443, 3.310)	.0002	2.257 (1.490, 3.419)	.0001	2.337 (1.542, 3.543)	<.0001	2.310 (1.523, 3.503)	<.0001	
nSES			1.187 (1.083, 1.301	0.0003	1.167 (1.065, 1.280)	.0010	1.136 (1.035, 1.247)	.0072	
TTR*nSES									0.5765
HBB	1.768 (1.288, 2.2426)	.0004	1.787 (1.302, 2.454)	.0003	1.787 (1.301, 2.455)	.0003	1.901 (1.383, 2.614)	<.0001	
nSES			1.191 (1.085, 1.307)	.0002	1.135 (1.034, 1.246)	.0078	1.101 (1.002, 1.210)	0.0459	
HBB*nSES									0.1210

Model 1: (Base model) adjusting for age sex and principal components of ancestry
Model 2: Base model + nSES
Model 3: Base model + nSES + diabetes + hypertension
Model 4: Base model + nSES + diabetes + hypertension +smoking + physical activity +alcohol
Model 5: Examining the statistical interaction between risk variant and nSES

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