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The Effect of Race on Factor VIII and von Willebrand Factor Levels After Adjustment for Covariates

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2007

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An abstract of
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Abstract

The Effect of Race on Factor VIII and von Willebrand Factor Levels After Adjustment for Covariates

By Amanda B Payne

Increased levels of Factor VIII (FVIII) and von Willebrand Factor (VWF) have been associated with risk of thrombosis . The proteins are acute-phase reactants, with levels increasing in response to physiologic stress. Levels of FVIII and VWF have also been associated with race. This report assesses the association of FVIII and VWF levels with race after adjustment for covariates associated with factor level and race. Data obtained from a control population from a large case-control study were analyzed to determine the most precise estimate of the association of race and factor levels. The most precise estimate of the effect of race on FVIII levels was determined to be a function of age, sex, CRP, fibrinogen, APTT, ABO type, prevalent diabetes, hormone replacement therapy use, average alcohol consumption, and percent of time spent sitting at work. The estimate of effect of race after adjustment was 0.10847 (0.07130-0.14564) ln(IU/dl). The most precise estimate of the effect of race on VWF levels was determined to be a function of age, sex, fibrinogen, APTT, ABO type, education level attainment, average alcohol consumption, and duration of smoking. The estimate of effect of race was 0.06745(0.02108-0.11382) ln(IU/dl). Race remained a significant predictor of levels after adjustment for both FVIII and VWF models. Future studies are needed to further characterize the association of factor levels with race and to assess the relationship of factor levels with risk of thrombosis.

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Introduction:

Cardiovascular disease is a leading cause of morbidity and mortality in the United States[1]. Racial/ethnic disparities in the prevalence of both venous and arterial thrombosis have been reported[2]. For example, the risk of idiopathic venous thrombosis is 1.3 times higher for African Americans compared to Caucasians[3], and the risk of ischemic stroke is 2.4 times higher for African Americans compared to Caucasians[2]. Although a growing body of research has emerged attempting to explain these racial disparities, the underlying associations remain unclear.

Increased levels of procoagulant proteins Factor VIII (FVIII) and von Willebrand Factor (VWF) have been associated with increased risk of both venous and arterial thrombosis[4]. FVIII circulates in plasma bound to VWF and is proteolytically cleaved during clot formation to yield activated FVIII which serves as a cofactor for the activation of Factor X. Subsequently, activated Factor X serves as a cofactor for the conversion of prothrombin to thrombin, which acts on fibrinogen to form a fibrin clot. VWF stabilizes FVIII, regulates FVIII activity, and provides an adhesive linkage between platelets and the subendothelium at sites of vascular injury.

Because FVIII and VWF are acute-phase reactants, circulating levels are often increased in response to physiologic stress. Increased levels of both proteins have been associated with conditions such as diabetes[5, 6], malignancy[7], and pregnancy[8]. Non-O blood group[9], oral contraceptive use[10], increasing age[11], and sex[12] have also been associated with increased levels of both FVIII and VWF. Of particular interest, ethnic differences in mean steady-state factor levels have been reported, with African Americans having higher average levels of both FVIII and VWF[9].

Racial disparity associated with the risk of thrombotic disease could partially be explained by the difference in factor levels between racial/ethnic groups. However, the association between race and factor level is not well understood and could be driven by a differential distribution of a combination of environmental, biologic, or genetic predictors between racial/ethnic groups. The goal of this study is to examine the association between race and average levels of FVIII and VWF after adjusting for environmental and biologic predictors of level. This information will inform future work regarding potential variables underlying ethnic disparities in thrombotic disease risk.

Methods:

Study Population

The Genetic Attributes and Thrombosis Epidemiology (GATE) methods have been described elsewhere[13]. Briefly, GATE is a matched case-control study designed to determine predictors of risk of venous thromboembolism. Cases (n=1145) were selected from patients presenting with a first or recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) at either Crawford Long Hospital or Emory University Hospital in Atlanta, Georgia. Control subjects were sampled from an Emory Healthcare primary care clinic in Atlanta, Georgia. The control group (n=1309) was sampled to be similar to cases in age, sex, and race distributions. For this report, black and white control subjects not currently receiving anticoagulant therapy and with available FVIII and VWF data were analyzed (n=1231). This project was approved by the Emory University Institutional Review Board.

Variable Selection

Variables selected for analysis were chosen based on a literature search conducted between February 18, 2010 and July 30, 2010. Peer-reviewed publications reporting associations of covariates with race, FVIII and/or VWF levels were evaluated. The results of this search are reported in **Table 1**.

Demographic Variables

Age, race, sex, annual household income, and education level attainment were obtained using data from a standardized questionnaire. All variables were self-reported.

Health-Related Variables

Health-related variables were derived from standardized questionnaire responses. BMI was derived from self-reported weight and height. Exposure to adrenergic stimuli, prevalent inflammation, prevalent hypercholesterolemia, oral contraception usage and hormone replacement therapy usage were derived from self-reported current medication usage (prescription and over-the-counter). Prevalent cardiovascular disease, kidney disease, diabetes, hypertension, hyperthyroidism, liver disease, infectious disease, post-menopausal status, recent surgery, and active malignancy were determined by self-report.

Lifestyle Variables

Lifestyle variables were derived from standardized questionnaire responses. Average alcohol consumption and duration of smoking were determined by self-report. Physical activity was derived by calculating metabolic equivalents (1 MET =1kcal/kg/hour) expended on average per month using self-reported physical activity data. METs were calculated using a method defined by the World Health Organization[14]. Percent time sitting at work was derived from self-reported time spent sitting while at a

particular job. Total percent time sitting was defined as the total amount of time sitting divided by the total time at work.

Laboratory Variables

Blood samples were collected from control subjects at the CDC Division of Blood Disorders Laboratory (Atlanta, Georgia). Blood for laboratory tests was collected in siliconized evacuated glass tubes (Vacutainer, Becton Dickinsom and Company, Franklin Lakes, New Jersey) containing 0.109M sodium citrate in a 1 to 9 volume ratio of sodium citrate to blood. The blood was centrifuged at 1,600 x g at 4 ºC for 20 minutes followed by repeat centrifugation of the separated plasma using the same protocol. The resulting platelet-poor plasma was stored in 0.5-mL aliquots at -70 ºC until testing.

Factor VII, Factor VIII, APTT, and Fibrinogen were measured on the STA coagulation analyzer (Diagnostica Stago, Parsippany, New Jersey). Factor VII clotting activity was measured using Factor VII-deficient plasma (Diagnostica Stago) and Neoplastin CI+ (Diagnostica Stago) and expressed as International Units per deciliter (IU/dl) by comparison with the International Standard for FVII (National Institute for Biological Standards and Control, Potters Bar, Hertfordshire). Factor VIII clotting activity was determined using a one-stage assay (Diagnostica Stago) using silica as an activator and was expressed as IU/dl by comparison with the International Standard for FVIII and VWF (National Institute for Biological Standards and Control, Potters Bar, Hertfordshire). APTT was measured via the STA-PTT A kit (Diagnostica Stago) using silica as an activator. Fibrinogen was quantified using the STA-Fibrinogen kit (Diagnostica Stago) based on the clotting method of Clauss[15]. Von Willebrand Factor antigen was measured by ELISA using polyclonal antiserum (Diagnostica Stago) and

expressed as IU/dl by comparison with the International Standard for FVIII and VWF (National Institute for Biological Standards and Control, Potters Bar, Hertfordshire). C-Reactive Protein (CRP) was measured using a sandwich Enzyme Immuno Assay (ALPCO Diagnostics, Salem, New Hampshire). ABO serotype was determined using the reverse-typing method with A1 and B Referencells (Immucor, Norcross, Georgia).

Statistical Analysis

FVIII and VWF were log-transformed to yield a more normal distribution. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Bivariate analyses assessing the association of race with each of the covariates were conducted using the chi-square test for categorical covariates and t-test for continuous covariates. Bivariate analyses assessing the relationship between lnFVIII and lnVWF with each of the covariates were performed using simple least squares regression.

Multivariate analyses assessing the association of race with each of the covariates adjusting for age and sex were conducted using logistic regression. Multivariate analyses assessing the association of each of the covariates with lnFVIII and lnVWF adjusting for age and sex were performed using least squares regression.

Separate least squares regression models were developed to assess the impact of race on FVIII and VWF after adjustment for covariates collected using a standardized method. Initially, the model contained all covariates associated with both lnFVIII (or lnVWF) and race as well as race x covariate interaction terms. Due to the correlation between lnVWF and lnFVIII, the factors were not included in the respective lnFVIII and lnVWF models in order to more accurately assess differences in mean factor levels by race. Collinearity diagnostics were used to assess possible collinearity between

covariates and interaction terms. Any term with VIF>10 and/or condition index>30 and associated proportion of variation for two covariates>0.5 was dropped from the model[16]. Interaction was assessed using the partial f-test on the resulting model. Confounding was assessed by modeling all possible subsets of the model resulting from the interaction assessment (Full Model). The model yielding a race parameter estimate within 10% of the Full Model with the most precision was chosen as the Final Model. Adjusted means were calculated based on this final model. For comparison purposes, lnVWF was added to the lnFVIII Final Model and, likewise, lnFVIII was added to the lnVWF Final Model in order to show how adding each of the correlates to the respective models would influence the assessment of the effect of race on each of the factors.

In order to assess the statistical association of each of the factors with race after adjustment for covariates in the Final Models, separate logistic regression analyses were conducted for each of the respective models with race being the outcome measure. Log-Likelihood measures were used to determine the impact of adding and removing lnFVIII and lnVWF from the models, effectively measuring their association with race after adjustment for other covariates.

Results:

Bivariate Analyses

As indicated by the results in **Table 2**, race is associated with the outcomes of interest (FVIII and VWF). Other clinical variables such as FVII, CRP, fibrinogen, APTT, and ABO type are also associated with race as well as health history variables such as prevalent cardiovascular disease, prevalent diabetes, oral contraceptive use, hormone replacement therapy use, prevalent hypertension, and prevalent infectious

disease. Several demographic and lifestyle variables were also associated with race, including age, BMI, sex, annual household income, education level attainment, average alcohol consumption, physical activity, and percent of time sitting at work. Bivariate analyses of covariates associated with lnFVIII (**Table 3**) indicate lnFVIII level is associated with laboratory variables such as lnVWF, CRP, fibrinogen, APTT, and ABO type. lnFVIII level was also found to be associated with health history variables such as prevalent hypercholesterolemia, prevalent cardiovascular disease, menopause status, prevalent kidney disease, prevalent diabetes, and prevalent hypertension as well as demographic and lifestyle variables such as age, BMI, sex, annual household income, education level attainment, average alcohol consumption, and percent of time spent sitting at work. Bivariate analyses of covariates associated with lnVWF (**Table 3**) indicate lnVWF level is associated with laboratory variables such as lnFVIII, FVII, CRP, fibrinogen, APTT, and ABO type. lnVWF level was also found to be associated with health history variables such as prevalent hypercholesterolemia, menopause status, prevalent kidney disease, prevalent diabetes, and prevalent hypertension as well as demographic and lifestyle variables such as age, BMI, annual household income, education level attainment, average alcohol consumption, duration of smoking, and percent of time spent sitting at work.

Multivariate Analyses

FVIII

Covariates associated with both lnFVIII and race given age and sex included CRP, fibrinogen, APTT, ABO type, prevalent cardiovascular disease, prevalent diabetes, hormone replacement therapy use, prevalent hypertension, BMI, annual household income, education level attainment, average alcohol consumption, and percent of time spent sitting at work (**Table 4**).

The initial model contained these covariates as well as age, sex, and covariate x race interaction terms. Collinearity diagnostics indicated the fibrinogen x race, APTT x race, BMI x race, annual household income x race, education level attainment x race, average alcohol consumption x race, and age x race interaction terms contributed to collinearity in the model. These terms were subsequently removed. The partial f-test for overall interaction indicated no significant statistical interaction (p>0.20). Thus, the Full Model was:

$$\begin{aligned} lnFVIII = \alpha &+ \beta_1(Race) + \beta_2(Age) + \beta_3(Sex) + \beta_4(CRP) + \beta_5(Fibrinogen) + \beta_6(APTT) \\ &+ \beta_7(ABO1) + \beta_8(ABO2) + \beta_9(ABO3) + \beta_{10}(Cardiovascular\ Disease) \\ &+ \beta_{11}(Diabetes) + \beta_{12}(HRT) + \beta_{13}(Hypertension) + \beta_{14}(BMI) \\ &+ \beta_{15}(Household\ Income) + \beta_{16}(Education) + \beta_{17}(Alcohol\ Consumption) \\ &+ \beta_{18}(\%\ Sitting) + \epsilon \end{aligned}$$

The estimate of β_1 for the Full Model was 0.10 (CI: 0.06-0.14). All possible subsets of covariates of this model (keeping race, age, and sex in the model) were analyzed to determine the model yielding the most precise estimate of the race parameter. The resulting model was:

$$\begin{aligned} lnFVIII = \alpha &+ \beta_1(Race) + \beta_2(Age) + \beta_3(Sex) + \beta_4(CRP) + \beta_5(Fibrinogen) + \beta_6(APTT) \\ &+ \beta_7(ABO1) + \beta_8(ABO2) + \beta_9(ABO3) + \beta_{10}(Diabetes) + \beta_{11}(HRT) \\ &+ \beta_{12}(Alcohol\ Consumption) + \beta_{13}(\%\ Sitting) + \epsilon \end{aligned}$$

The estimate of β_1 for the Final Model was 0.11 (CI: 0.07-0.15). As can be noted in **Figure 1**, this indicates that adjusting for covariates associated with both lnFVIII and race, given age and sex, results in a reduction in the mean difference in FVIII between African Americans and Whites (mean difference=15.96 IU/dl). This reduction is shown in comparison to the mean FVIII differences computed using a crude model that makes no adjustments (mean difference=25.34 IU/dl) and a model adjusting for only age and sex (mean difference=25.82 IU/dl). Addition of lnVWF to the Final Model results in much larger decrease in mean differences (mean difference=6.74 IU/dl). This is likely due to the strong association of lnVWF with race and its high correlation with lnFVIII.

Logistic regression analyses (**Table 5**) assessing the association of lnFVIII with race indicated that even after adjustment for other covariates, lnFVIII was still statistically associated with race.

VWF

Covariates associated with both lnVWF and race given age and sex included CRP, fibrinogen, APTT, ABO type, prevalent diabetes, hormone replacement therapy use, prevalent hypertension, BMI, annual household income, education level attainment, average alcohol consumption, and duration of smoking (**Table 4**). The initial model contained these covariates as well as age, sex, and covariate x race interaction terms. Collinearity diagnostics indicated the fibrinogen x race, APTT x race, BMI x race, annual household income x race, education level attainment x race, average alcohol consumption x race, and age x race interaction terms contributed to collinearity in the model. These terms were subsequently removed. The partial f-test for overall interaction indicated no significant statistical interaction ($p>0.20$). Thus, the Full Model was:

$$\begin{aligned} lnVWF = \alpha &+ \beta_1(Race) + \beta_2(Age) + \beta_3(Sex) + \beta_4(CRP) + \beta_5(Fibrinogen) + \beta_6(APTT) \\ &+ \beta_7(ABO1) + \beta_8(ABO2) + \beta_9(ABO3) + \beta_{10}(Diabetes) + \beta_{11}(HRT) \\ &+ \beta_{12}(Hypertension) + \beta_{13}(BMI) + \beta_{14}(Household\ Income) + \beta_{15}(Education) \\ &+ \beta_{16}(Alcohol\ Consumption) + \beta_{17}(Duration\ of\ Smoking) + \epsilon \end{aligned}$$

The estimate of β_1 for the Full Model was 0.06 (CI: 0.01-0.11). All possible subsets of covariates of this model (keeping race, age, and sex in the model) were analyzed to determine the model yielding the most precise estimate of the race parameter. The resulting model was:

$$\begin{aligned} lnVWF = \alpha &+ \beta_1(Race) + \beta_2(Age) + \beta_3(Sex) + \beta_4(Fibrinogen) + \beta_5(APTT) + \beta_6(ABO1) \\ &+ \beta_7(ABO2) + \beta_8(ABO3) + \beta_9(Education) + \beta_{10}(Alcohol\ Consumption) \\ &+ \beta_{11}(Duration\ of\ Smoking) + \epsilon \end{aligned}$$

The estimate of β_1 for the Final Model was 0.07 (CI: 0.02-0.11). As can be noted in **Figure 1**, this indicates that adjusting for covariates associated with both lnVWF and race, given age and sex, results in a reduction in the mean difference in VWF between African Americans and Whites

(mean difference=8.74 IU/dl). This reduction is shown in comparison to the mean VWF differences computed using a crude model that makes no adjustments (mean difference=17.52 IU/dl) and a model adjusting for only age and sex (mean difference=19.08 IU/dl). Addition of lnFVIII to the Final Model results in much larger decrease in mean differences (mean difference=-0.25 IU/dl). This is likely due to the association of lnFVIII with race and its high correlation with lnVWF.

Logistic regression analyses (**Table 5**) assessing the association of lnVWF with race indicated that even after adjustment for other covariates, lnVWF was still statistically associated with race.

Discussion:

The objective of this study was to assess the association between race and FVIII and VWF levels after adjustment for environmental and biologic predictors of level in a control population recruited in Atlanta, Georgia. The results of bivariate analyses for this study indicate race is associated with several previously reported predictors of FVIII and VWF levels, including CRP, ABO type, prevalent diabetes, and prevalent hypertension. Bivariate analyses also confirmed FVIII and VWF levels were associated with many of the previously reported predictors of level. Multivariate analyses of predictors associated with both race and factor level after adjustment for age and sex indicated the most precise estimate of the effect of race on FVIII level was produced by a model containing age, sex, CRP, fibrinogen, APTT, ABO type, prevalent diabetes, HRT use, average alcohol consumption, and the amount of time spent sitting at work. After adjustment, the mean difference in FVIII level between African Americans and Caucasians dropped from 25.34 IU/dl (crude model) to 15.96 IU/dl. Similarly, the most precise estimate of the effect of race on VWF level was produced by a model containing age, sex, fibrinogen, APTT,

ABO type, education level attainment, average alcohol consumption, and duration of smoking. After adjustment, the mean difference in VWF level between African Americans and Caucasians dropped from 17.52 IU/dl (crude model) to 8.74 IU/dl. Analysis of logistic models of the association of covariates with race constructed based on the Final Models for FVIII and VWF using Likelihood Ratio measures (**Table 5**) indicate both are significantly associated with race after adjustment for other covariates, with FVIII being more statistically significantly associated with race than VWF. Log-Likelihood statistics indicate that removal of lnVWF from the model results in a larger p-value than removal of lnFVIII.

The bivariate associations between factor levels and covariates largely agreed with the literature. With the exception of smoking duration in the VWF analyses, all associated covariates had been previously reported to affect factor levels (**Table 1**). Several variables previously reported to be associated with factor level did not indicate a statistically significant association with factor levels in this population, including prevalent hyperthyroid disease, prevalent infectious disease, and prevalent inflammation. These covariates may not be associated with race in this population due to insufficient statistical power.

Although adjustment for known predictors of factor levels resulted in a decrease in the mean difference in factor levels between African Americans and Caucasians, race still remained a significant predictor of levels. Several covariates in **Table 1** were unmeasured in this study, including hormone levels, ratio of high-density lipoproteins to low-density lipoproteins, markers of hemolysis, and time of day factor level was measured. It is plausible that addition of these covariates to the models could account for

more of the difference in factor levels between groups. Differences in level could also be explained by unmeasured genetic covariates, both factor-specific and pathway-specific. Several DNA polymorphisms have been found within the genes coding for FVIII[17] and VWF[18-20] that have been shown to be associated with factor levels. Genetic variants within other genes in the pathway of production and secretion of FVIII[21] and VWF[22, 23] have also been shown to affect factor levels. Interaction between these and other as yet undiscovered DNA variants, which may differ in their frequency by race, could contribute to the association of factor level with race.

Researchers have suggested using race-specific reference ranges for FVIII and VWF in clinical laboratories[24] when diagnosing disorders related to these factors. This report found insufficient evidence to suggest differences by race could be explained by the presented models and that adjustment based on these models could allow the use of one reference range. The distribution of adjusted factor levels for Caucasians and African Americans based on the Final Models and comparison to crude models are presented in **Figure 2** along with reference ranges. These distributions indicate a shift in normal FVIII and VWF levels between the two groups, highlighting the need for race-specific reference ranges.

Because adjustment for covariates did not fully explain differences in factor levels by race, it is conceivable that some of the difference in risk of thrombosis between the groups could be explained by variability in factor levels. However, it is unclear whether or not the reduced difference after adjustment would account for much of the differences in risk, as recent reports on racial disparities in thrombosis risk have found novel

biomarkers for risk, such as FVIII and VWF, did not considerably alter the relationship of risk and race[25-27].

Strengths and Limitations

This analysis utilizes a large control population of African American and Caucasian subjects collected for a case-control analysis of venous thrombosis. The large size of the control population allowed for the effective analysis of differences in variables by race. The case-control study was designed to measure biologic, genetic, and environmental determinants of thrombosis risk. For this analysis, all variables were collected in a standardized manner. Laboratory variables were collected using standardized laboratory techniques and health history and lifestyle variables were collected using a uniform questionnaire. The large number of covariates analyzed for this report allowed a thorough assessment of the associations of interest and led to development of a precise model of the covariates affecting factor levels.

The results of this analysis may not be generalizable to the US population. The control population was selected based on the age, sex, and race distribution of cases. This distribution is likely different from the general population. However, there is evidence to suggest this control population is similar to other cohorts collected for studying cardiovascular issues[28] (**Table 6**). The Caucasian portion of the study population has a similar distribution of age, sex, and prevalent disease as the other cohorts.

Several of the variables, such as VWF and CRP, had considerable missing data. However, analyses of measures of effect of race on FVIII and VWF after adjustment for age and sex using the subset of data with no missing values was not different from the

full dataset (data not shown). This suggests that, although the models incorporating variables with missing data may have been analyzed using smaller numbers of subjects than other models, the missingness should not bias the estimates of interest.

A standardized questionnaire was used to assess several of the covariates used in this study. Similar to any study using self-report, the classification of some of the covariates may be incorrect. This could alter the association of the covariate with the outcome of interest, causing the calculated association to be an incorrect representation of the true effect. Of particular interest are the self-reported health history variables, as reporting of a history of disease diagnosis may be incorrect due to either recall bias or misdiagnosis. It is likely several of these variables are under-reported. This misclassification would hamper our ability to adjust correctly for confounders.

Future Analyses

This analysis indicates the differences in FVIII and VWF levels between African Americans and Caucasians can partially be explained by differences in covariates associated with both race and factor levels. However, race still remains a significant predictor of factor levels. Future studies to further characterize the nature of this association are needed. Studies assessing unmeasured biologic, environmental, and genetic covariates could help researchers understand this association. Future studies are also needed to assess the relationship of factor levels and race with thrombosis risk using adjusted models, as it remains unclear if these adjusted models would help explain some of the disparities in thrombosis risk.

Tables:

	FVIII	VWF
COVARIATE	ABO[9, 29-36]	ABO[9, 29, 30, 32, 33, 35, 37-39]
	ADRENERGIC STIMULI[35]	ADRENERGIC STIMULI[35]
	AGE[11, 12, 30, 34, 35, 40-42]	AGE[11, 30, 35, 41]
	BMI[11, 34, 41-44]	BMI[11, 41, 44]
	CHOLESTEROL[43]	CHOLESTEROL[45]
	CARDIOVASCULAR DISEASE[35, 42, 46-50]	CARDIOVASCULAR DISEASE[25, 35, 47-53]
	CIRCADIAN VARIATION[54]	CIRCADIAN VARIATION[55]
	MENSTRUAL CYCLE DAY*[56]	MENSTRUAL CYCLE DAY*[56]
	ALCOHOL CONSUMPTION[11, 43]	ALCOHOL CONSUMPTION[11]
	APTT[44]	APTT[44]
	EDUCATION LEVEL[11]	EDUCATION LEVEL[11]
	HDL*[11, 42-44]	HDL*[11, 44]
	HORMONE LEVEL*[11, 43]	MENOPAUSE STATUS[57]
	MENOPAUSE STATUS[11]	PHYSICAL ACTIVITY[11]
	PHYSICAL ACTIVITY[11, 43]	ESTROGEN THERAPY[30, 35, 56]
	SMOKING STATUS[11, 42]	FIBRINOGEN[44]
	ESTROGEN THERAPY[10, 34, 35, 56]	FVII[44]
	FIBRINOGEN[12, 34, 44]	FVIII[44]
	FVII[44]	GLUCOSE*[44]
	GLUCOSE*[42-44]	DIABETES[5, 11, 35, 41]
	HEMOLYSIS*[34]	HYPERTENSION[57, 58]
	DIABETES[5, 6, 11, 34, 35, 41, 42]	HYPERTHYROID DISEASE[35]
	HYPERTENSION[42, 43]	INFECTION[35]
	HYPERTHYROID DISEASE[34, 35]	LIVER DISEASE[35]
	INFECTION[35]	MALIGNANCY[35]
	INFLAMMATION[34]	NEUROLOGIC STRESS*[35]
	LDL*[43]	PREGNANCY*[8, 35]
	LIVER DISEASE[34, 35]	RACE[9, 11, 24, 25, 30, 32, 35, 40, 41, 49, 59-62]
	MALIGNANCY[7, 34, 35]	RENAL DISEASE[35]
	NEUROLOGIC STRESS*[35]	RESPIRATORY FAILURE*[35]
	PREGNANCY*[8, 34, 35]	SOCIOECONOMIC STATUS[62-64]
	RACE[6, 9, 11, 12, 30-32, 34-36, 40-42, 49, 59-61, 65-67]	SEX[40, 41, 59]
	RENAL DISEASE[34, 35, 68]	TRIGLYCERIDES*[11, 44]
	RESPIRATORY FAILURE*[35]	WHR*[11, 44]
	SOCIOECONOMIC STATUS[63, 64, 69]	
	SEX[11, 12, 34, 40-42, 59]	
	SURGERY[34]	
	TRIGLYCERIDES*[11, 34, 43]	
	VWF[33, 34, 44]	
	WBC*[43]	
	WHR*[11, 44]	

Table 1: Results of literature review of covariates associated with race, FVIII and/or VWF levels (*not measured in dataset)

	Race		
Clinical Variables	***Caucasian***	***African American***	
	Mean		P
ln(Factor VIII)(n=1231)	4.8945	5.0682	<.0001
ln(Von Willebrand Factor)(n=1003)	4.7991	4.9339	<.0001
Factor VII (n=1231)	127.5	121.9	0.0154
CRP (n=1130)	2.92	4.85	<.0001
Fibrinogen (n=1230)	3.35	3.72	<.0001
APTT (n=1231)	28.21	28.7	0.0082
	N		P
	%		
ABO Type			
.	6	5	
	0.91%	0.87%	
A	268	158	
	40.73%	27.57%	
AB	23	27	
	3.50%	4.71%	<.0001
B	77	121	
	11.70%	21.12%	
O	284	262%	
	43.16%	45.72	
Demographic Variables			
	Mean		P
Age (n=1231)	50.16	47.92	0.0019
BMI (n=1231)	26.58	30.17	<.0001
	N		P
	%		
Sex			
Female	284	341	
	43.16%	59.51%	<.0001
Male	374	232	
	56.84%	40.49%	
Annual Household Income			
.	2	2	
	0.30%	0.35%	
<$10,000	2	31	
	0.30%	5.41%	
$10,000-$24,999	24	85	
	3.65%	14.83%	<0.0001
$25,000-$39,999	71	148	
	10.79%	25.83%	
$40,000-$54,999	84	105	
	12.77%	18.32%	
$55,000-$69,999	103	93	
	15.65%	16.23%	
>$70,000	372	109	
	56.53%	19.02%	
Education Level			
6th Grade or Less	0	5	
	0.00%	0.87%	
7th-11th Grade	7	45	
	1.06%	7.85%	
High School Graduate	31	96	
	4.71%	16.75%	<.0001
Some College or Technical School	137	196	
	20.82%	34.21%	
Junior College Graduate	44	37	
	6.69%	6.46%	
College Graduate	174	109	
	26.44%	19.02%	
Post-Graduate Work	265	85	
	40.27%	14.83%	
Lifestyle Variables			
	N		P
	%		
Average Alcohol Consumption - Current			
>20 Drinks/Week	17	8	
	2.58%	1.40%	
8-20 Drinks/Week	82	10	
	12.46%	1.75%	<.0001
1-7 Drinks/Week	250	119	
	37.99%	20.77%	
<1 Drinks/Week	120	116	
	18.24%	20.24%	
Rarely/Never	189	320	
	28.72%	55.85%	
	Mean		P
Duration of Smoking (n=1231)	8.24	9.21	0.1991
Physical Activity (METs Expended/Month)(n=1231)	103	72.16	<.0001
% Time Sitting at Work (n=1231)	52.11	41.78	<.0001

	Race		
Health History Variables	***Caucasian***	***African American***	
	N		P
	%		
Exposure to Adrenergic Stimulus			
No	600	532	
	91.19%	92.84%	0.2856
Yes	58	41	
	8.81%	7.16%	
Prevalent Hypercholesterolemia			
No	547	498	
	83.13%	86.91%	0.0647
Yes	111	75	
	16.87%	13.09%	
Prevalent Cardiovascular Disease			
No	635	536	
	96.50%	93.54%	0.0161
Yes	23	37	
	3.50%	6.46%	
Post-Menopause (females only)			
.	3	4	
	1.06%	1.17%	
No	154	197	0.653
	54.23%	57.77%	
Yes	127	140	
	44.72%	41.06%	
Prevalent Kidney Disease			
.	1	1	
	0.15%	0.17%	
No	653	564	0.3712
	99.24%	98.43%	
Yes	4	8	
	0.61%	1.40%	
Prevalent Diabetes			
No	619	484	
	94.07%	84.47%	<.0001
Yes	39	89	
	5.93%	15.53%	
OC User (females only)			
No	235	303	
	82.75%	88.86%	0.028
Yes	49	38	
	17.25%	11.14%	
HRT User (females only)			
No	196	283	
	69.01%	82.99%	<.0001
Yes	88	58	
	30.99%	17.01%	
Active Malignancy			
No	654	571	
	99.39%	99.65%	0.5154
Yes	4	2	
	0.61%	0.35%	
Prevalent Hypertension			
No	469	307	
	71.28%	53.58%	<.0001
Yes	189	266	
	28.72%	46.42%	
Prevalent Hyperthyroidism			
No	643	555	
	97.72%	96.86%	0.3505
Yes	15	18	
	2.28%	3.14%	
Prevalent Infectious Disease			
No	464	452	
	70.52%	78.88%	0.0008
Yes	194	121	
	29.48%	21.12%	
Prevalent Inflammation – Medication Indication			
No	637	556	
	96.81%	97.03%	0.8202
Yes	21	17	
	3.19%	2.97%	
Prevalent Liver Disease			
No	651	572	
	98.94%	99.83%	0.0528
Yes	7	1	
	1.06%	0.17%	
Recent Surgery			
No	641	563	
	97.42%	98.25%	0.3165
Yes	17	10	
	2.58%	1.75%	

Table 2: Association between race and various potential covariates of FVIII and VWF

	ln(FVIII)		ln(VWF)	
Clinical Variables				
	Mean	P-Value	Mean	P-Value
Factor VIII			*(n=1003)*	
3.64≤FVIII≤4.74			4.5	<.0001
4.74<FVIII≤4.98			4.78	
4.98<FVIII≤5.22			4.99	
FVIII>5.22			5.21	
Von Willebrand Factor	*(n=1003)*			
3.14≤VWF≤4.61	4.6			
4.61<VWF≤4.88	4.87			
4.88<VWF≤5.12	5.07	<.0001		
VWF>5.12	5.29			
Factor VII	(n=1231)		(n=1003)	
40≤FVII≤100	4.97		4.82	
100<FVII≤119	4.95		4.81	
119<FVII≤141	5.02	0.3634	4.87	0.0139
FVII>141	4.96		4.92	
CRP	(n=1130)		(n=910)	
0≤CRP≤0.720	4.91		4.78	
0.720<CRP≤1.820	4.93		4.84	
1.820<CRP≤4.320	5.02	<.0001	4.91	<.0001
CRP>4.320	5.1		4.94	
Fibrinogen	(n=1230)		(n=1003)	
0.85≤Fibrinogen≤2.96	4.84		4.74	
2.96<Fibrinogen≤3.43	4.91		4.81	
3.43<Fibrinogen≤3.96	5.01	<.0001	4.89	<.0001
Fibrinogen>3.96	5.14		5.02	
APTT	(n=1231)		(n=1003)	
20.8≤APTT≤26.4	5.11		5.03	
26.4<APTT≤28.1	5.01		4.86	
28.1<APTT≤30.2	4.95	<.0001	4.84	<.0001
APTT>30.2	4.83		4.7	
ABO Type	(n=1220)		(n=1000)	
A	5.03		4.92	
AB	5.15		5.01	
B	5.15	<.0001	5.05	<.0001
O	4.85		4.73	
Health History Variables				
Exposure to Adrenergic Stimulus	(n=1231)		(n=1003)	
No	4.98		4.87	
Yes	4.93	0.1947	4.82	0.2553
Prevalent Hypercholesterolemia	(n=1231)		(n=1003)	
No	4.96		4.85	
Yes	5.06	0.0005	4.96	0.0017
Prevalent Cardiovascular Disease	(n=1231)		(n=1003)	
No	4.97		4.86	
Yes	5.1	0.0044	4.95	0.0959
Post-Menopause	(n=1224)		(n=996)	
No	4.95		4.85	
Yes	5.06	<.0001	4.92	0.0124
Prevalent Kidney Disease	(n=1229)		(n=1001)	
No	4.97		4.86	
Yes	5.33	0.0006	5.19	0.0056
Prevalent Diabetes	(n=1231)		(n=1003)	
No	4.95		4.84	
Yes	5.16	<.0001	5.04	<.0001
OC User	(n=1231)		(n=1003)	
No	4.98		4.87	
Yes	4.94	0.277	4.83	0.421
HRT User	(n=1231)		(n=1003)	
No	4.97		4.86	
Yes	4.99	0.5363	4.88	0.5097
Active Malignancy	(n=1231)		(n=1003)	
No	4.98		4.86	
Yes	5.03	0.708	5.07	0.191
Prevalent Hypertension	(n=1231)		(n=1003)	
No	4.93		4.82	
Yes	5.06	<.0001	4.94	<.0001
Prevalent Hyperthyroidism	(n=1231)		(n=1003)	
No	4.98		4.86	
Yes	4.87	0.0881	4.81	0.4346
Prevalent Infectious Disease	(n=1231)		(n=1003)	
No	4.96		4.86	
Yes	4.99	0.285	4.86	0.8712
Prevalent Inflammation – Medication Indication	(n=1231)		(n=1003)	
No	4.97		4.86	
Yes	5.07	0.0885	4.97	0.0843
Prevalent Liver Disease	(n=1231)		(n=1003)	
No	4.98		4.86	
Yes	4.64	0.0072	4.89	0.8596
Recent Surgery	(n=1231)		(n=1003)	
No	4.98		4.86	
Yes	4.98	0.9749	4.81	0.5471

	ln(FVIII)		ln(VWF)	
Demographic Variables				
Age	(n=1231)		(n=1003)	
20≤Age≤40	4.9		4.81	
40<Age≤50	4.94		4.78	
50<Age≤60	5	<.0001	4.9	<.0001
Age>60	5.05		4.96	
BMI	(n=1231)		(n=1003)	
16.40≤BMI≤23.80	4.89		4.77	
23.80<BMI≤27.10	4.93		4.85	
27.10<BMI≤31.5	5.01	<.0001	4.93	<.0001
BMI>31.5	5.06		4.91	
Sex	(n=1231)		(n=1003)	
Female	5.01		4.88	
Male	4.94	0.0002	4.85	0.222
Annual Household Income	*(n=1227)*		*(n=999)*	
<$10,000	5.14		4.98	
$10,000-$24,999	5.07		4.95	
$25,000-$39,999	5.02		4.9	
$40,000-$54,999	4.99	<.0001	4.9	<.0001
$55,000-$69,999	4.93		4.82	
>$70,000	4.93		4.82	
Education Level	(n=1231)		(n=1003)	
6th Grade or Less	4.99		5.17	
7th-11th Grade	5.15		5	
High School Graduate	5.07		4.98	
Some College or Technical School	5		4.88	
Junior College Graduate	5.04	<.0001	4.91	<.0001
College Graduate	4.93		4.84	
Post-Graduate Work	4.91		4.77	
Lifestyle Variables				
Average Alcohol Consumption - Current	(n=1231)		(n=1003)	
>20 Drinks/Week	4.78		4.7	
8-20 Drinks/Week	4.84		4.75	
1-7 Drinks/Week	4.93		4.8	
<1 Drinks/Week	4.99	<.0001	4.86	<.0001
Rarely/Never	5.04		4.94	
Duration of Smoking	(n=1231)		(n=1003)	
0≤Smoking Duration≤15	4.98	4.84		
Smoking Duration>15	4.97	0.1057	4.89	0.0006
Physical Activity (METs Expended/Month)	(n=1231)		(n=1003)	
0	4.99		4.87	
0<Physical Activity≤48	4.97		4.89	
48<Physical Activity≤128	4.98	0.1849	4.86	0.2176
Physical Activity >128	4.95		4.83	
% Time Sitting at Work	(n=1231)		(n=1003)	
0≤Time Sitting≤8	5.05		4.92	
8<Time Sitting≤50	4.96		4.85	
50<Time Sitting≤80	4.94	0.0006	4.86	0.0076
Time Sitting>80	4.95		4.81	

Table 3: Association between lnFVIII and lnVWF an their covariates

Covariate	ln(Factor VIII) p-value	ln(von Willebrand Factor) p-value	Race p-value
FVII	0.1874	0.5224	0.0057
CRP	**<.0001**	**0.0016**	<.0001
Fibrinogen	**<.0001**	**<.0001**	<.0001
APTT	**<.0001**	**<.0001**	0.0035
ABO Type	**<.0001**	**<.0001**	0.0004
Exposure to Adrenergic Stimulus	0.4212	0.7783	0.1436
Prevalent Hypercholesterolemia	0.0217	0.023	0.72
Prevalent Cardiovascular Disease	**0.0175**	0.5229	0.001
Menopause Status	0.2629	0.2066	0.6093
Prevalent Kidney Disease	0.0064	0.0181	0.2381
Prevalent Diabetes	**<.0001**	**<.0001**	<.0001
Oral Contraceptive Use	0.8613	0.9529	0.0009
Hormone Replacement Therapy Use	**0.0088**	**0.0389**	0.0004
Active Malignancy	0.7618	0.8754	0.8987
Prevalent Hypertension	**<.0001**	**0.014**	<.0001
Prevalent Hyperthyroid Disease	0.1233	0.5033	0.5364
Prevalent Infectious Disease	0.8415	0.7866	<.0001
Prevalent Inflammation	0.2698	0.2787	0.9121
Prevalent Liver Disease	0.0003	0.5613	0.1059
Recent Surgery	0.3711	0.7313	0.3629
BMI	**<.0001**	**0.0002**	<.0001
Annual Household Income	**<.0001**	**0.0005**	<.0001
Education Level Attainment	**<.0001**	**<.0001**	<.0001
Average Alcohol Consumption	**<.0001**	**<.0001**	<.0001
Duration of Smoking	0.8257	**0.0341**	0.0067
Physical Activity	0.3312	0.3037	<.0001
Percent of Time Sitting at Work	**0.0144**	0.0806	<.0001

Table 4: Age- and sex-adjusted associations of covariates with the outcomes and race

Test	FVIII Model: $logit(P(race)) = \alpha + \beta_1(Age) + \beta_2(Sex) + \beta_3(CRP) + \beta_4(Fibrinogen) + \beta_5(APTT) + \beta_6(ABO1) + \beta_7(ABO2) + \beta_8(ABO3) + \beta_9(Diabetes) + \beta_{10}(HRT) + \beta_{11}(Alcohol\ Consumption) + \beta_{12}(\%\ Sitting) + \beta_{13}(lnFVIII) + \beta_{14}(lnVWF) + \epsilon$	VWF Model: $logit(P(race)) = \alpha + \beta_1(Age) + \beta_2(Sex) + \beta_3(Fibrinogen) + \beta_4(APTT) + \beta_5(ABO1) + \beta_6(ABO2) + \beta_7(ABO3) + \beta_8(Education) + \beta_9(Alcohol\ Consumption) + \beta_{10}(Duration\ of\ Smoking) + \beta_{11}(lnFVIII) + \beta_{12}(lnVWF) + \epsilon$
Remove lnVWF	P=0.0054	P=<.0001
Remove lnFVIII	P=<.0001	P=<.0001
Remove lnVWF lnFVIII	P=<.0001	P=<.0001

Table 5: Results of logistic regression analysis assessing the association of FVIII and VWF with race using Likelihood Ratio Statistics

Variable	ARIC	B58C	CHS	FHS	GATE
% Men	47.1	50	39.2	42.7	56.8
Age	54.3	44.9	72.3	54.5	50.1
BMI	27	27.4	26.3	27.4	26.6
Prevalent CVD	6.7	NA	0	6.5	3.5
Prevalent Diabetes	8.5	1.9	25.8	7.9	5.9
Prevalent Hypertension	27.2	4.2	34.9	16.9	28.7
FVII	116	NA	123	99	127.5
VWF	105	117	NA	121	130.3
FVIII	121	NA	115	NA	141.6

Table 6: [28]Comparison of Caucasian subjects in GATE to other cohorts of cardiovascular studies. ARIC: Atherosclerosis Risk in Communities; B58C: British 1958 Birth Cohort; CHS: Cardiovascular Health Study; FHS: Framingham Heart Study

Figures:

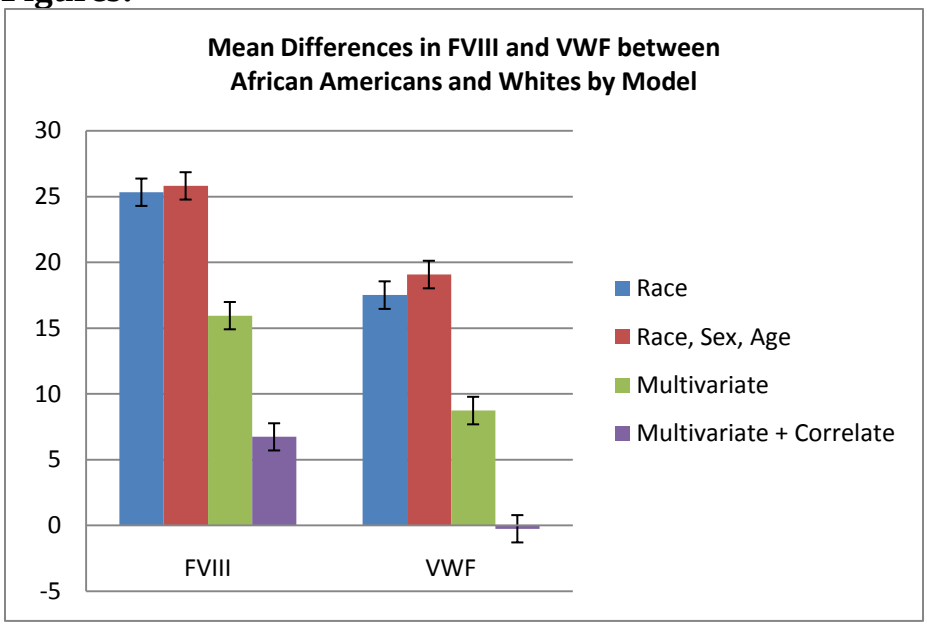

Figure 1: Mean Differences between African Americans and Whites in FVIII and VWF by model

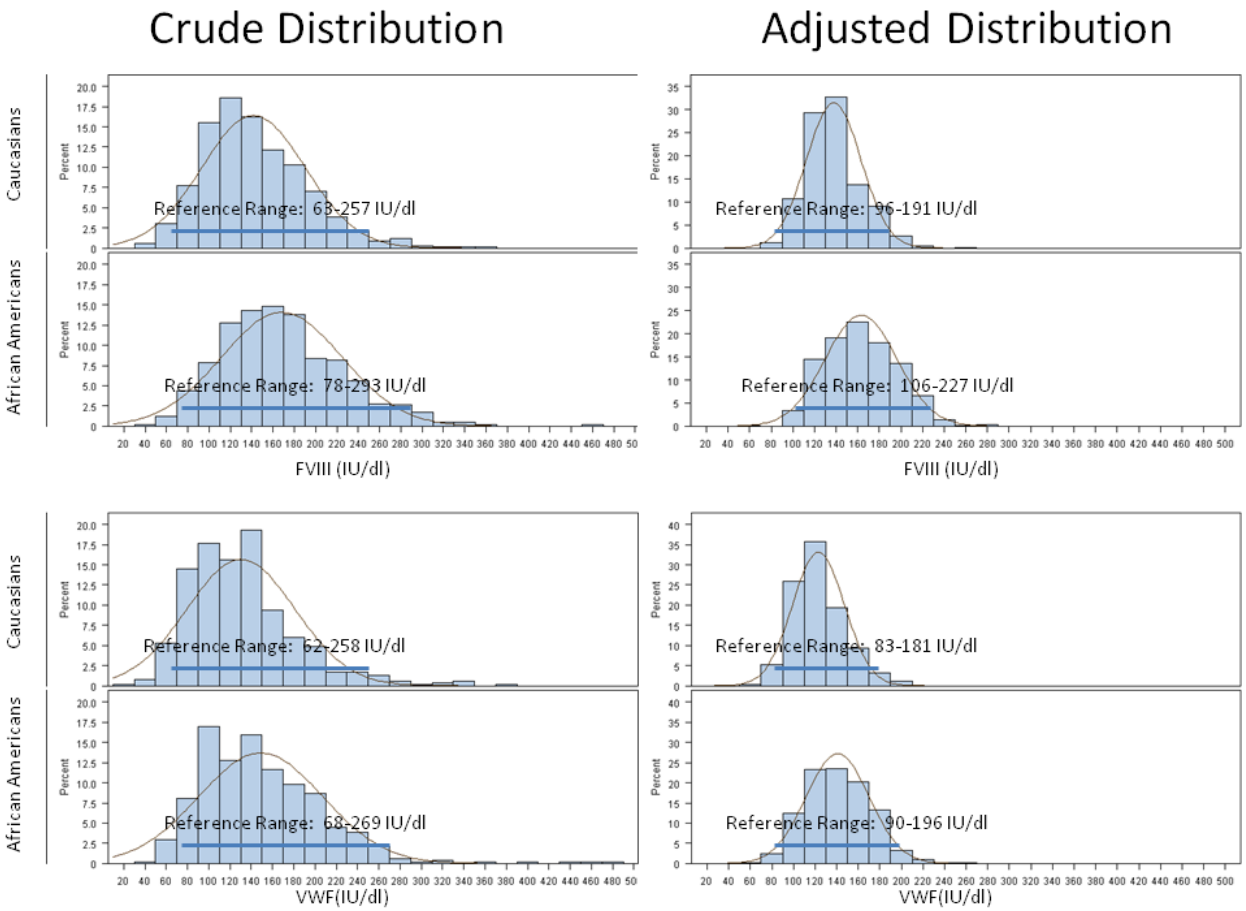

Figure 2: Distribution of crude and adjusted FVIII and VWF levels by race with associated reference ranges

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