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## GENDER DIFFERENCES IN THE ENDOTHELIAL FUNCTION OF UNTREATED HYPERTENSION

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### Abstract

Vascular endothelial dysfunction is associated with increased risk for adverse cardiovascular events. However, less is known about gender differences in the endothelial function of untreated hypertensive individuals. The purpose of this study was to assess endothelial function in women and men with untreated hypertension. Ninety participants (35 women, 55 men), aged 40 to 60 years (mean age, 46.1±8.2 years), with untreated stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) underwent brachial artery endothelial-dependent flow-mediated dilation and endothelial-independent glyceryl trinitrate dilation. Women had a smaller flow-mediated dilation response than men (adjusted means±SEM; 1.8%±0.6 vs. 3.9%±0.4,  $p=.036$ ). adjusting for baseline arterial diameter ( $p=.004$ ), age ( $p=.596$ ), ethnicity ( $p=.496$ ), log shear stress ratio ( $p<.001$ ), BMI ( $p=.009$ ), 24-hour DBP ( $p=.169$ ), HDL ( $p=.225$ ), log creatinine ( $p=.927$ ) and log physical activity ( $p=.682$ ). Glyceryl trinitrate dilation did not differ by gender in adjusted models. Women between the ages of 40 and 60 years with untreated stage 1 hypertension exhibited a greater impairment of endothelial function compared to their male counterparts. These findings raise the possibility that female gender may impart a greater risk of cardiovascular events in patients with untreated stage 1 hypertension potentially due to poorer endothelial function.

### Keywords

endothelial dysfunction; flow-mediated dilation; hypertension; gender differences; brachial artery

## INTRODUCTION

Gender differences are often observed in the prevalence, presentation and outcome of the various cardiovascular conditions.<sup>1–4</sup> Hypertension is an established cardiovascular risk factor. The SYMPHONY<sup>4</sup> and INTERHEART<sup>5, 6</sup> studies have reported a higher prevalence of hypertension in women, compared to men, presenting with acute coronary syndromes<sup>4</sup> and a stronger association between hypertension and risk of first myocardial infarction in women than in men,<sup>5</sup> especially among women less than 60 years of age.<sup>6</sup> Taken together these findings suggest that hypertension may confer greater cardiovascular risk for women than for men. The reasons for these gender differences are not entirely clear.

Endothelial dysfunction, as indicated by impaired flow mediated dilation (FMD), is characteristic of hypertension<sup>7-9</sup> and is associated with poor outcomes in hypertensive patients.<sup>10</sup> The effect of gender on FMD has been examined in various populations and has been reported inconsistently in the literature.<sup>14, 15, 11, 12, 13</sup> To our knowledge gender differences in FMD in untreated hypertensive individuals have not been examined. Given that hypertension may be a stronger cardiovascular risk factor for women, especially among women less than 60 years of age,<sup>6</sup> the purpose of this study was to compare FMD in women and men with untreated hypertension, in order to explore the possibility that hypertension in women may be accompanied by a more marked impairment of FMD than for men.

## METHODS

### Participants

The study included ninety participants (35 women, 55 men), between 40 to 60 years of age (mean age,  $46.1 \pm 8.2$  years), with stage 1 hypertension (SBP 140–159 mm Hg and/or diastolic (D) BP 90–99 mm Hg) who had not been treated with antihypertensive medications in the preceding 12 months. The presented study sample was drawn from a larger study population that also included participants with pre-hypertension that was conducted at Duke University Medical Center (DUMC) from 2004 through 2007.<sup>14</sup> As previously described,<sup>14</sup> exclusion criteria were body mass index (BMI)  $> 35 \text{ kg/m}^2$ ; diabetes mellitus; pacemaker; atrial fibrillation; myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery within 6 months of enrollment; heart failure; severe uncorrected primary valvular disease; uncorrected thyroid heart disease; oral contraceptive use; pregnancy; hormone replacement therapy; alcohol or drug abuse within 12 months; renal or hepatic dysfunction; dementia; inability to comply with the assessment procedures; or unwillingness to provide informed consent. Individuals with previously diagnosed obstructive sleep apnea or identified with the Berlin Questionnaire<sup>15</sup> as high risk of sleep apnea syndrome were excluded given the association between obstructive sleep apnea and impaired endothelial function.<sup>16</sup>

Participants were recruited by advertisements in the Piedmont region of North Carolina that includes a general population of over one million that reside within a 30 mile radius of Duke University Medical Center. The study protocol was approved by the Institutional Review Board at Duke University Medical Center. All eligible individuals provided written informed consent prior to participation in the study.

### Demographic, Anthropometric and Biochemical Assessment

Data were collected on age, gender, height, weight, BMI, ethnicity, cigarette smoking, and alcohol consumption. Blood samples were collected in the morning after an overnight fast. Specimens were analyzed by Labcorp using automated enzymatic assays for glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides, immunochemiluminometric assay for high sensitivity C-reactive protein (CRP) and electrochemiluminescence immunoassay for follicle-stimulating hormone (FSH) among women. The self-reported date of last menstrual period was used to determine premenopausal women's menstrual cycle phase, with 50% of women determined to be in the luteal phase, 33% in the follicular phase and 17% in the menstrual phase.

### Blood Pressure Assessment

Clinic BP was determined on three visits, each approximately 1-week apart. On each occasion, BP was measured after 5-minutes seated in a quiet, temperature-controlled room. Four BP readings, each 2-minutes apart, were taken using a mercury sphygmomanometer

and stethoscope. The last 3 readings for each visit, a total of 9 readings, were used to represent mean clinic SBP and DBP.

24-hour ambulatory BP was assessed with the Oscar 2 ambulatory BP monitor (Suntech Medical, Raleigh, NC)<sup>17</sup> on 3 weekdays, each approximately 1 week apart. ABP readings were reviewed and artifact edited as previously described.<sup>18</sup>

### Physical Activity Assessment

Daytime physical activity was assessed with the Mini-Mitter Actiwatch wrist-watch style actigraphy (Mini-Mitter, Sunriver, OR). The actigraph was worn on the wrist for each of the 3 ABP monitoring days, and averaged to provide a mean physical activity score.

### Vascular Endothelial Function Assessments

Vascular studies of the brachial artery were assessed in the morning, following an overnight fast. Longitudinal B-mode images of the brachial artery, in the region 4 to 6 cm anterior to the antecubital fossa, were recorded and stored digitally using a 7–11 MHz linear-array transducer and Aspen ultrasound system. Images were captured: (a) after 10 minutes of supine rest, (b) during the first 120 seconds of reactive hyperemia, achieved by inflation of a pneumatic occlusion forearm cuff to supra-systolic pressure (~200mmHg) for 5 minutes, (c) after a second rest period of 15 minutes, and (d) during the 3–6 minute period after administration of 400mcg sublingual glyceryl trinitrate (GTN), used to induce non-endothelial-dependent arterial dilation. End-diastolic images were stored and arterial diameters measured as the distance between the proximal and distal arterial wall intima-media interfaces using PC-based software (Brachial Analyzer - Version 5.0, Medical Imaging Applications LLC, Iowa City, Iowa). Peak FMD response was assessed from 10–120 seconds post-deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting. Endothelial dependent FMD and endothelial independent GTN dilation (GTND) were expressed as absolute diameter change (maximum arterial diameter-baseline arterial diameter) and percent increase in arterial diameter ((maximum arterial diameter-baseline arterial diameter/baseline arterial diameter)× 100%), which is the index that has been adopted most widely.<sup>19</sup> The percent change index may result in bias towards greater FMD in smaller arteries and in arteries experiencing greater shear stress.<sup>19, 20</sup> Therefore, FMD was examined using baseline arterial diameter and shear stress as covariates. Shear stress was calculated as using the formula described by Mitchell et al.<sup>21</sup> (shear stress =  $8 \times \mu \times V / \text{baseline arterial diameter}$ ) at baseline and during reactive hyperemia, with  $\mu$  representing assumed blood viscosity (0.035 dyne×s/cm<sup>2</sup>), V representing velocity (cm/s) and baseline arterial diameter in cm. Shear stress ratio was calculated by dividing hyperemic shear stress/baseline shear stress. Shear stress ratio was used as an index of the hyperemic shear stress stimulus for FMD.<sup>21</sup>

All studies were completed by the same sonographer who has over 10 years of experience in performing vascular assessments in our lab. We have previously reported<sup>22</sup> that our lab's repeated FMD assessments on 20 healthy women and men over two consecutive days showed a correlation of  $r=.81$ ,  $p<.001$ , a mean difference of  $0.6 \pm 2.7\%$ , and a coefficient of variation of 26.7%.

### Statistical Analysis

Normality statistics (skew, kurtosis, Kolmogorov-Smirnov), histograms, boxplots and normal probability plots were examined to assess normality. Non-normal variables underwent log base-e transformation (triglycerides, serum creatinine, creatinine clearance, baseline shear stress, hyperemic shear stress, shear stress ratio and physical activity), square root transformation (GTND) or trimming at the 95<sup>th</sup> percentile to prevent excessive

influence of outliers (glucose); CRP remained non-normally distributed and non-parametric testing was used. Fifty-four percent of participants did not consume alcohol therefore the number of alcoholic beverages consumed in the past week variable was dichotomized into 0 alcoholic beverages and 1 or more alcoholic beverages.

Data are expressed as mean $\pm$ SD for continuous normally distributed variables or median (interquartile range) for non-normally distributed continuous variables. T-tests (for normal distributions) or the Wilcoxon rank sum test (for non-normal distributions) were used to compare gender differences in continuous variables.  $\chi^2$  tests were used to assess differences in categorical variables between female and male participants. Analysis of covariance (ANCOVA) tests were used to evaluate the effect of gender on FMD and GTND. Based on previous research, covariates included in the planned model were baseline arterial diameter,<sup>7</sup> age,<sup>23</sup> ethnicity,<sup>7</sup> and shear stress (for FMD analysis).<sup>21</sup> In secondary confirmatory analysis, the presence of a univariate correlation between the variable of interest and FMD and GTND was performed. Variables were entered into the planned model if the univariate correlation between each variable and outcome variable (FMD or GTND) was  $p \leq .2$ . The equal variance ANOVA assumption was confirmed with non-significant Levene's tests. Women were classified as postmenopausal if they had amenorrhea for at least 1 year and serum FSH levels  $> 40$  IU/L. Statistical analyses were conducted using the SAS 9.2 system (SAS Institute, Cary, NC) with significance set at  $p \leq .05$ .

## RESULTS

### Sample Characteristics

Table 1 describes the participant characteristics. HDL cholesterol was higher among female participants ( $n=35$ ) when compared to male participants ( $n=55$ ). Men exhibited higher DBP, triglycerides, and glucose. There were 15 current smokers (6 women and 9 men) and 18 former smokers (7 women and 11 men). Women and men did not differ in the number of years they currently smoked ( $22.3 \pm 14.2$  years vs.  $18.0 \pm 13.4$  years,  $p=.535$ ), formerly smoked ( $14.8 \pm 8.2$  years vs.  $10.2 \pm 5.5$  years,  $p=.169$ ) or the number of years since they quit smoking ( $12.2 \pm 8.1$  years vs.  $15.7 \pm 7.3$  years,  $p=.353$ ). Two men and two women were taking cholesterol lowering medications. Ten women (28.6%) were classified as postmenopausal. Postmenopausal women were older ( $53.8 \text{ yrs} \pm 4.1$  vs.  $44.5 \text{ yrs} \pm 6.6$ ,  $p < .001$ ) and less likely to be African American (30% vs. 80%,  $p=.015$ ) than premenopausal women. Unadjusted vascular assessments of the brachial artery are presented in Table 2.

### Flow-Mediated Dilatation by Gender

The effect of gender on FMD was evaluated with ANCOVA (Table 3a). FMD was significantly impaired in female participants compared to male participants (adjusted means  $\pm$ SEM;  $1.4\% \pm 0.6$  vs.  $4.0\% \pm 0.4$ ,  $p=.002$ ). A gender by race interaction was not significant when included in the model.

In secondary confirmatory analysis (Table 3b), BMI, HDL cholesterol, 24-hour DBP, log serum creatinine and log physical activity correlated with FMD at  $p \leq .2$  (Table 4) and were entered into the planned ANCOVA model. In the final model (Figure 1), women continued to display a smaller FMD response than men (adjusted means $\pm$ SEM;  $1.8\% \pm 0.6$  vs.  $3.9\% \pm 0.4$ ,  $p=.036$ ). A gender by race interaction was not significant when included in the model. FMD did not differ by menopausal status in the planned and fully adjusted models.

### Glyceryl Trinitrate Dilatation by Gender

Baseline arterial diameter and ethnicity were significant determinants of sqrtGTND (Table 5a). SqrtGTND was not significantly different between women and men (adjusted means

$\pm$ SEM;  $3.8\% \pm 0.2$  vs.  $4.1\% \pm 0.1$ ,  $p=.121$ ). A gender by race interaction was not significant when included in the model.

In secondary confirmatory analysis (Table 5b), BMI, HDL cholesterol, LDL cholesterol, log triglycerides, glucose, 24-hour SBP, log creatinine clearance, alcohol drinker, and 24-hour HR correlated with sqrtGTND at  $p < .2$  (Table 4) and were entered into the planned ANCOVA model. Women and men did not differ on sqrtGTND (adjusted means $\pm$ SEM;  $3.4\% \pm 0.3$  vs.  $3.9\% \pm 0.2$ ,  $p=.072$ ). A gender by race interaction was not significant when included in the model. Results did not differ based on menopausal status in the planned and fully adjusted models.

## DISCUSSION

In this study, women between the ages of 40 and 60 years with untreated stage 1 hypertension exhibited poorer endothelial function, as indicated by smaller brachial artery FMD responses, compared to their male counterparts. In contrast, non-endothelium dependent vasodilation, assessed by the GTND response, was comparable between genders supporting the interpretation that women with hypertension exhibit an impairment of vascular endothelial function rather than a generalized vascular smooth muscle dysfunction.<sup>24</sup> These findings may be particularly relevant given that women have a higher sensitivity threshold than men for impaired FMD being indicative of the presence of CAD<sup>11</sup> and that reduced endothelial function has been found to be associated with an increased risk of cardiovascular events in women without CAD but not men.<sup>12</sup>

In accordance with the results of the current study, FMD was lower in women compared to men after adjustment for baseline artery diameter in 2265 adults (aged 24–39 years) participating in The Cardiovascular Risk in Young Finns Study.<sup>25</sup> In a subgroup analysis of 224 pairs of women and men matched for identical baseline artery diameter, men continued to show larger FMD responses than women ( $8.2\% \pm 4.7$  vs  $7.1\% \pm 4.7$ ,  $p=.004$ ) even after adjustment for traditional cardiovascular risk factors.<sup>25</sup> However, not all studies have reported similar gender differences in FMD responses. In healthy men and women FMD has been reported to be inversely related to age,<sup>23</sup> with men experiencing a progressive decline in endothelial function after age 40, while women exhibited a more dramatic age-related decline in their early 50's.<sup>26</sup> In a community sample (mean age  $61 \pm 9$  years), women demonstrated greater FMD responses than men up until 70 years of age;<sup>23</sup> a study of older adults (mean age;  $74.5 \pm 13.1$  years) reported relatively impaired endothelial responses in women compared to men;<sup>27</sup> and no gender differences in FMD responses were observed among individuals (mean age;  $62 \pm 12$  years) undergoing angiographic evaluation of CAD.<sup>12</sup> These inconsistent findings suggest that age, population under study (clinical versus community), treatment with cardiovascular medications and adjustment for baseline artery diameter may play a role in the inconsistencies observed in the literature regarding gender-based differences in endothelial function. Our present findings in a middle aged (mean age  $46 \pm 8$  years) sample of untreated hypertensive women and men suggest that hypertension may also moderate the association between endothelial function and gender.

Anand and colleagues<sup>6</sup> explored gender differences in cardiovascular risk factors using the INTERHEART database and found that hypertension was more strongly associated with first myocardial infarction in women (OR: 2.95; 95% CI: [2.66–3.28]) than in men (OR: 2.32; 95% CI: [2.16–2.48]) and the relationship was stronger for women less than 60 years of age (OR: 4.00; 95% CI: [3.31–4.84]) compared to older women (OR: 2.84; 95% CI: [2.49–3.23]). The reasons for this gender disparity are not known but our present observations raise the possibility that hypertension may impart an increased cardiovascular risk in women because of its association with poorer endothelial function. In addition,

because hypertension is less prevalent in younger (<45 years) women compared to men,<sup>28</sup> the presence of hypertension in younger women may be indicative of more extensive impairment of endothelial function.

Although hypertension is an established cardiovascular risk factor that is associated with endothelial dysfunction,<sup>7-9</sup> the mechanisms accounting for our observations of reduced endothelial function among hypertensive women remain to be clarified. Given that women have smaller conduit arteries than men,<sup>29, 30</sup> it is possible that over time similar pressures in smaller arteries may have a more profound effect on the endothelium. On the other hand, high BP may be a manifestation of more severe endothelial dysfunction in women, requiring more vascular disease to “overcome” the tendency of women to have lower BP. Palatini and colleagues<sup>31</sup> reported that untreated stage 1 hypertensive premenopausal women between 18 and 45 years of age had an increased risk of developing hypertensive end-organ damage (microalbuminuria and left ventricular hypertrophy) than men of the same age despite lower 24-hour SBP, BMI, triglycerides and glucose. The authors hypothesized that the negative consequences of a hypertensive BP may be greater for younger women given their general tendency to have lower BP than men of similar ages. Donahue et al.<sup>32</sup> also examined biomarkers of endothelial function (E-selectin and soluble intracellular adhesion molecule-1) in women and men who progressed from normoglycemia to pre-diabetes. The female participants who developed pre-diabetes exhibited poorer endothelial function than the normoglycemic controls while no differences were found among the male participants. The authors suggest that the pre-diabetic state may diminish the cardioprotective effect of being female, predisposing women to greater cardiovascular risk than their male counterparts. In the present study, untreated hypertension may also play a similar role in negating the cardioprotective advantage among women.

Women have often been viewed as being at lower cardiovascular risk due to the presence of cardioprotective reproductive hormones during the premenopausal years. However, gender-specific differences exist in CVD.<sup>1-4, 33</sup> Hypertension is more prevalent in younger (< 45 years) men and older (> 65 years) women<sup>28</sup> and women more commonly have hypertension when diagnosed with acute coronary syndromes.<sup>4</sup> The INTERHEART researchers reported that younger (< 60 years) hypertensive women had a greater risk of myocardial infarction than their older counterparts.<sup>6</sup> ENREF 7 In addition, Gierach et al.<sup>34</sup> found that among women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia, SBP and pulse pressure were stronger risk factors for CAD in premenopausal women compared to postmenopausal women. The findings reinforce the need for enhanced CVD risk assessment and management in all hypertensive women.

## LIMITATIONS

The present study must be interpreted within the context of its potential limitations. Vascular function assessments of premenopausal women were not measured at the same menstrual cycle phase. FMD responses fluctuate throughout the menstrual cycle being lowest during the menstrual phase.<sup>35</sup> Only 17% of premenopausal women in this study were assessed in their menstrual phase and therefore it is unlikely to account for our findings. It should be noted that chronic periodontal disease is associated with impaired endothelial function.<sup>36, 37</sup> Periodontal disease was not assessed in the current investigation and it is possible that such recognized and other currently unrecognized confounding factors may have played a role in the study findings. Strengths of the study include the large percentage of African American participants and younger women with hypertension.

## CONCLUSIONS

Hypertension is a major risk factor for CVD and CVD-related mortality in both men and women. Gender disparities in BP control and CVD risk management may exist, in part, due to an underestimation of women's CVD risk. Our data suggest that women with high BP may exhibit poorer endothelial function compared to their male counterparts. This observation may reflect greater subclinical CVD among younger hypertensive women, and support a more careful assessment and BP management for hypertensive women. Our present observations raise the possibility that female gender may impart an increased risk of cardiovascular events in those with untreated stage 1 hypertension because of its association with endothelial dysfunction. Additional studies are needed to confirm our findings and to examine potential mechanisms contributing to the greater endothelial dysfunction in women with untreated stage 1 hypertension.

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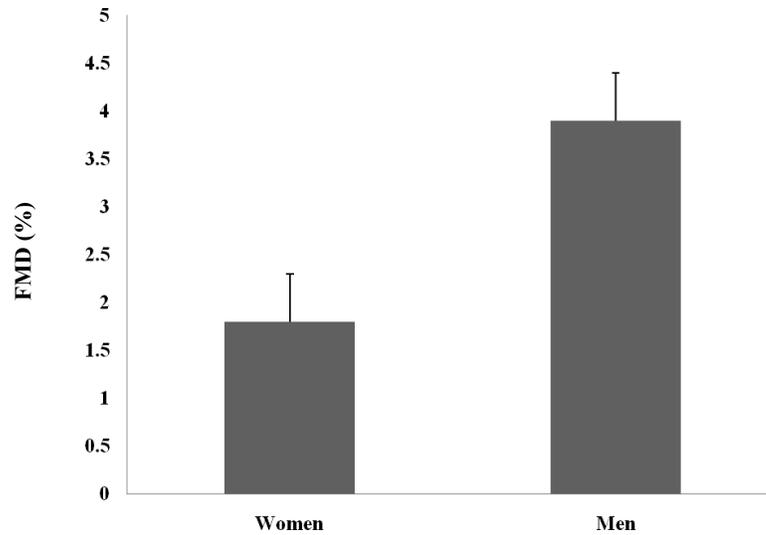
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**Figure 1.** Flow-mediated dilation (FMD) responses in women and men with untreated stage 1 hypertension  
FMD means adjusted baseline arterial diameter, age, ethnicity, log shear stress ratio, BMI, 24-hour DBP, HDL, log serum creatinine and log physical activity.

Table 1

## Participant characteristics

	Sample (n=90)	Women (n=35)	Men (n=55)	p
Age (yrs)	46.1 ± 8.2	47.2 ± 7.3	45.5 ± 8.8	.343
BMI (kg/m <sup>2</sup> )	28.8 ± 3.5	28.1 ± 4.1	29.2 ± 3.1	.178
Clinic SBP (mmHg)	143.0 ± 7.3	143.2 ± 7.3	142.9 ± 7.3	.860
Clinic DBP (mmHg)	91.9 ± 4.5	90.3 ± 4.9	92.9 ± 3.9	<b>.005</b>
24-hour SBP (mmHg)	134 ± 11	134 ± 12	135 ± 10	.600
24-hour DBP (mmHg)	81 ± 8	81 ± 9	82 ± 7	.785
24-hour HR (bpm)	76 ± 9	79 ± 9	74 ± 8	<b>.010</b>
Total Cholesterol (mg/dL)	196.9 ± 34.0	194.4 ± 33.7	198.6 ± 34.4	.572
HDL (mg/dL)	54.7 ± 16.5	62.8 ± 19.1	49.5 ± 12.3	<b>&lt;.001</b>
LDL (mg/dL)	117.5 ± 27.4	112.7 ± 29.4	120.6 ± 25.8	.189
Triglycerides (mg/dL)	99.5 (71.0–150.0)	76.0 (55.0–117.0)	116.0 (85.0–183.0)	<b>&lt;.001</b>
Glucose* (mg/dL)	94.1 ± 9.9	90.2 ± 9.9	96.6 ± 9.1	<b>.002</b>
CRP (mg/L)	1.3 (0.6–3.5)	1.4 (0.6–3.5)	1.2 (0.6–3.7)	.928
Serum Creatinine (mg/dL)	0.9 (0.8–1.0)	0.7 (0.7–0.8)	1.0 (0.9–1.1)	<b>&lt;.001</b>
Creatinine Clearance (ml/min)	113.9 (100.4–137.4)	104.0 (88.9–131.9)	119.8 (104.3–143.1)	<b>.036</b>
Ethnicity (% AA)	55.6	65.7	49.1	.122
Current Smoker (%)	17.2	17.6	17.0	.936
Former Smoker (%)	20.7	20.6	20.8	.985
Current or Former Smoker (%)	37.9	38.2	37.7	.963
1 Alcoholic Beverage(s) in the Past Week (%)	46.1	42.9	48.2	.645
Physical Activity (units)	94209.4 (72997.3–127092.1)	104019.4 (81308.0–141331.4)	84710.2 (62760.9–111016.4)	<b>.011</b>

For continuous variables, data are mean ± SD or median (interquartile range) for normally distributed and non-normally distributed data respectively. For categorical variables, data are relative frequencies (percentages).

AA= African Americans; BMI = body mass index; CRP = C reactive protein; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure.

\* trimmed 95%

**Table 2**

## Mean values of vascular assessments

	Sample (n=90)	Women (n=35)	Men (n=55)	<i>p</i>
<b>FMD Assessments</b>				
Baseline Artery Diameter (mm)	4.5 ± 0.7	3.9 ± 0.4	4.9 ± 0.6	<.001
Absolute FMD (mm)	0.13 ± 0.13	0.09 ± 0.1	0.16 ± 0.1	.014
FMD (%)	3.0 ± 2.9	2.4 ± 2.7	3.4 ± 3.0	.128
Baseline Shear Stress (dyne/cm <sup>2</sup> )	7.5 (6.0–9.7)	8.1 (6.6–9.8)	7.1 (5.7–9.5)	.129
Hyperemic Shear Stress (dyne/cm <sup>2</sup> )	39.7 (28.6–66.7)	45.0 (27.2–74.9)	39.0 (28.6–56.8)	.350
Shear Stress Ratio	6.1 (3.9–8.3)	6.1 (3.7–9.3)	6.1 (3.9–7.9)	.983
<b>GTND Assessments</b>				
Baseline Artery Diameter (mm)	4.4 ± 0.7	3.8 ± 0.5	4.8 ± 0.5	<.001
Absolute GTND (mm)	0.7 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	.252
GTND (%)	15.7 (13.0–19.9)	18.7 (15.0–25.4)	15.5 (11.3–17.4)	<.001

Data are mean ± SD or median (interquartile range) for normally distributed and non-normally distributed data respectively.

FMD = flow-mediated dilation; GTND = glyceryl trinitrate dilation.

**Table 3**

The effect of gender on FMD in planned and confirmatory ANCOVA models

3a. Planned Model						
	df	SS	Mean Square	F	p	Partial $\eta^2$
Model	5	299.3	59.9	11.2	<.001	0.40
Error	84	447.8	5.3			
Corrected Total	89	747.2				

	df	Type III SS	Mean Square	F	p	Partial $\eta^2$
Gender	1	57.2	57.2	10.7	.002	0.11
Ethnicity	1	6.0	6.0	1.1	.293	0.01
Age	1	0.9	0.9	0.2	.681	<0.01
Baseline Artery Diameter	1	41.4	41.4	7.8	.007	0.08
Log Shear Stress Ratio	1	226.2	226.2	42.4	<.001	0.34

3b. Confirmatory Model						
	df	SS	Mean Square	F	p	Partial $\eta^2$
Model	10	378.1	37.8	7.8	<.001	0.51
Error	75	362.1	4.8			
Corrected Total	85	740.2				

	df	Type III SS	Mean Square	F	p	Partial $\eta^2$
Gender	1	21.9	21.9	4.5	.036	0.06
Ethnicity	1	2.3	2.3	0.5	.496	<0.01
Age	1	1.4	1.4	0.3	.596	<0.01
Baseline Artery Diameter	1	43.2	43.2	8.9	.004	0.11
Log Shear Stress Ratio	1	252.3	252.3	52.3	<.001	0.41
BMI	1	34.9	34.9	7.2	.009	0.09
HDL	1	7.2	7.2	1.5	.225	0.02
24-hour DBP	1	9.3	9.3	1.9	.169	0.02
Log Creatinine	1	0.04	0.04	0.01	.927	0.00

	<i>df</i>	Type III SS	Mean Square	<i>F</i>	<i>p</i>	Partial $\eta^2$
Log Physical Activity	1	0.8	0.8	0.2	.682	<0.01

BMI = body mass index; DBP = diastolic blood pressure; FMD = flow-mediated dilation; HDL = high density lipoprotein; Log = log base-e; SS = sum of squares.

**Table 4**

Correlates of FMD and GTND in women and men with untreated stage 1 hypertension

	FMD		sqrtGTND	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Female/Male (0/1)	.16	.140	-.32	.002
Age (yrs)	-.12	.263	-.03	.750
BMI (kg/m <sup>2</sup> )	.17	.108	-.26	.012
Clinic SBP (mmHg)	-.12	.279	-.13	.220
Clinic DBP (mmHg)	-.16	.131	.02	.864
24-hour SBP (mmHg)	-.05	.619	-.18	.091
24-hour DBP (mmHg)	-.16	.142	-.08	.458
24-hour HR (bpm)	-.05	.672	.17	.109
Total Cholesterol (mg/dL)	-.07	.528	-.13	.214
HDL (mg/dL)	-.16	.123	.29	.007
LDL (mg/dL)	.02	.825	-.14	.188
Log Triglycerides (mg/dL)	.03	.791	-.37	<.001
Glucose* (mg/dL)	.10	.351	-.27	.009
CRP (mg/L)	.004	.973	-.12	.243
Log Serum Creatinine	.14	.185	-.20	.066
Log Creatinine Clearance	.06	.550	-.23	.030
White/AA Ethnicity (0/1)	-.01	.898	.11	.286
Current Smoker (No/Yes, 0/1)	-.05	.664	.02	.888
Former Smoker (No/Yes, 0/1)	.03	.814	-.01	.926
Current or Former Smoker (No/Yes, 0/1)	-.02	.835	-.002	.983
1 Alcoholic Beverage(s) in the Past Week	-.06	.550	.16	.146
Log Physical Activity (units)	-.15	.166	-.01	.962
Baseline Artery Diameter (mm)	-.08	.457	-.60	<.001
Log Baseline Shear Stress	.20	.064	n/a	n/a
Log Hyperemic Shear Stress	.61	<.0001	n/a	n/a
Log Shear Stress Ratio	.56	<.0001	n/a	n/a

Pearson's *r* correlations are presented for continuous variables normally distributed variables.

For categorical and non-normally distributed variables Spearman's *r* correlations are presented.

AA= African Americans; BMI = body mass index; CRP = C reactive protein; DBP = diastolic blood pressure; FMD = flow-mediated dilation; GTND = glyceryl trinitrate dilation; HDL = high density lipoprotein; HR = heart rate; LDL = low density lipoprotein; Log = log base-e; SBP = systolic blood pressure; sqrt = square root.

\* trimmed 95%

**Table 5**

The effect of gender on GTND in planned and confirmatory ANCOVA models

5a. Planned Model						
	df	SS	Mean Square	F	p	Partial $\eta^2$
Model	4	25.6	6.4	13.7	<.001	0.40
Error	84	39.3	0.5			
Corrected Total	88	64.9				

	df	Type III SS	Mean Square	F	p	Partial $\eta^2$
Gender	1	1.2	1.2	2.4	.121	0.03
Ethnicity	1	1.9	1.9	4.0	.047	0.29
Age	1	0.9	0.9	2.0	.164	0.02
Baseline Artery Diameter	1	16.4	16.4	35.0	<.001	0.05

5b. Confirmatory Model						
	df	SS	Mean Square	F	p	Partial $\eta^2$
Model	13	29.6	2.3	5.3	<.001	0.52
Error	68	29.4	0.4			
Corrected Total	81	59.0				

	df	Type III SS	Mean Square	F	p	Partial $\eta^2$
Gender	1	1.5	1.5	3.4	.068	0.05
Ethnicity	1	0.6	0.6	1.4	.250	0.26
Age	1	0.2	0.2	0.5	.498	0.01
Baseline Artery Diameter	1	9.8	9.8	22.6	<.001	0.01
BMI	1	0.2	0.2	0.5	.491	0.01
HDL	1	0.1	0.1	0.2	.671	<0.01
LDL	1	0.3	0.3	0.7	.400	<0.01
Log Triglycerides	1	0.7	0.7	1.6	.207	0.02
24-hour SBP	1	0.1	0.1	0.2	.694	<0.01
Glucose	1	1.0	1.0	2.4	.125	0.04

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	<i>df</i>	Type III SS	Mean Square	<i>F</i>	<i>p</i>	<i>Partial η</i> <sup>2</sup>
Log Creatinine Clearance	1	0.3	0.3	0.8	.375	0.02
Drinker (Y/N)	1	1.7	1.7	4.0	.050	0.04
24-hour HR	1	1.4	1.4	3.3	.075	0.04

BMI = body mass index; GTND = glyceryl trinitrate dilatation; HDL = high density lipoprotein; HR = heart rate; LDL = low density lipoprotein; Log = log base-e; SBP = systolic blood pressure; SS = sum of squares; sqrt = square root.