Published in final edited form as:

Maturitas. 2012 January ; 71(1): 70–75. doi:10.1016/j.maturitas.2011.10.012.

A genetic polymorphism in the *CYP19A1* gene and the risk of hypertension among midlife women

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Abstract

Objective—To test whether a synonymous single nucleotide polymorphism (A→G; rs700518) in the *CYP19A1* gene, which encodes the enzyme aromatase, is associated with an increased risk for hypertension of midlife women.

Methods—In a cross-sectional study, 639 midlife women were recruited. Eligible women had their blood pressure, weight and height measured, and donated a blood sample for hormone and genetic analyses. The participants also completed a detailed study survey. Women were categorized according to their genotype, blood pressure measurements, and medical history. The data were analyzed using logistic and linear regression models. The study had 80% power to detect differences in mean systolic blood pressure (SBP; 4.5 mmHg) and diastolic blood pressure (DBP; 3 mmHg).

Results—The selected polymorphism was significantly associated with hypertension and SBP in unadjusted analyses. Interestingly, women with hypertension were more likely to be homozygous for the A allele (AA) compared to women who were not categorized as having hypertension. Further, the mean SBP was significantly higher for women who were homozygous for the A allele when compared to women carrying the other genotypes (AG or GG). The unadjusted association between DBP values and genotype was of border line statistical significance ($p=0.07$). However, after adjustment for potential confounders, (age, race, body mass index (BMI), smoking and physical activity) the associations between genotype and hypertension/blood pressure were attenuated and not statistically significant.

Conclusion—The rs700518 polymorphism in the *CYP19A1* is not associated with hypertension in our sample of midlife women. Other factors, including race and BMI, appear to play a greater role.

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Authors' Disclosure Statements: No competing financial interests exist.

Competing Interest

The authors do not have any competing interests to declare.

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Keywords

CYP19A1; estrogen; polymorphism; hypertension; race; women

1. Introduction

Hypertension is a risk factor for cardiovascular morbidity and mortality, with a prevalence of nearly 26% worldwide[1,2]. It is estimated that by 2025, more than 1.5 billion individuals will have hypertension[3]. In fact, more American women die from hypertension and related complications than breast cancer[4]. Generally, in the U.S., the risk of hypertension increases significantly as women get older (mainly after their 5th decade of life), and is higher among African-American women than Caucasian women[5,6]. Additional risk factors for hypertension in women are cigarette smoking, excess adiposity, and family history[2,4,6].

During the menopausal transition, women undergo physiological changes, which may predispose them to develop hypertension [4]. One of the most prominent changes is a gradual decline in estrogen levels and a decline in the ratio of circulating estrogens to androgens. Estrogen, the main sex steroid hormone in the female reproductive system, has been shown to have a protective role in the cardiovascular system, primarily by facilitating vasodilation and decreasing the production of vasoconstrictor substances[1,7,8]. Thus, estrogen appears to be important for maintaining regular functioning of the cardiovascular system. Estrogen levels can be altered by many factors, including levels/activity of aromatase. Aromatase is the key enzyme that catalyzes the conversion of androgens to estrogens and consequently, it affects serum hormone levels and ratios. Aromatase activity and/or levels also can be altered as a result of polymorphisms in its coding gene *CYP19A1*.

Only a few studies have tested whether genetic variations in *CYP19A1* are associated with blood pressure and hypertension [1,9–11] and the results of these studies are inconsistent. Ramirez et al.[9] evaluated polymorphisms within the *CYP19A1* gene, *IVS4* (rs11575899), and *3'UTR*(rs10046); findings from this study suggested that the *CYP19A1* gene may be involved in the regulation of blood pressure in women only (independent of menopausal status). Specifically, the *3'UTR_11* and *IVS4_22* genotypes were associated with an increased risk of diastolic hypertension and the *IVS4_11* and *3'UTR_22* genotypes were associated with a decreased risk of systolic hypertension in non-obese women (body mass index; BMI<30 kg/m²) and not in obese women. In the Framingham Heart Study's offspring community-based cohort study, the single nucleotide polymorphism (SNP) rs4646 was associated with pulse pressure in men and diastolic blood pressure (DBP) in women[10]. However, in the same study, the SNP rs700518 was not associated with any of the selected blood pressure measurements[10]. Similarly, in a study by Ellis et al.[11], that was based on the Victorian Family Heart Study and included both sexes, no significant association was observed between blood pressure and the same SNP. Lastly, Shimodaira et al.[1]in a case-control study, assessed potential associations between five SNPs (rs1870049, rs936306, rs10046, rs4646 and rs700518) in *CYP19A1* and essential hypertension both in men and women. Significant differences between genotype distribution and the compared groups were found only after stratifying the sample by sex[1]. Specific to rs700518, women homozygous for the A allele(AA) and heterozygous (AG) had a greater risk of essential hypertension and higher systolic blood pressure (SBP) levels compared to women who were homozygous for the G allele(GG).

Therefore, the purpose of this study was to expand the limited findings from previously published studies on the potential associations between a synonymous SNP (rs700518) in

the *CYP19A1* gene and hypertension. The study specifically tested the hypothesis that the selected SNP is associated with the risk of hypertension in women aged 45 to 54 enrolled in a study of midlife health.

2. Materials and methods

2.1 Study sample

The parent study sample (n=639) was originally recruited for a cross-sectional study of midlife women, which was designed to examine risk factors for menopausal hot flashes. Sample methods have been previously described in detail elsewhere[12]. Briefly, between 2000 and 2004, recruitment letters were mailed to women aged 45 to 54 years residing in Baltimore city and the surrounding counties. Potential participants had to meet the following eligibility criteria[12]: women aged 45 to 54 years old, not taking hormonal therapy, not pregnant and no medical history of cancer. Further, because the study was designed to examine the health of women undergoing the menopausal transition, women were eligible only if they reported having at least three menstrual periods in the last 12 months. Therefore, all women in the study were either pre- or peri-menopausal. Eligible women were scheduled to come to the clinic during the morning hours and were instructed to fast overnight prior to the visit. During the clinic visit, each participant had their blood pressure, weight and height measured, and a blood sample was drawn for hormone and genetic analyses. The participants also completed the study survey, which included questions regarding demographic information, medical and family history, reproductive history, past exogenous hormone use, menopausal symptoms, and lifestyle habits (e.g. smoking, diet, etc.). All participants in this study gave written informed consent according to procedures approved by the University of Illinois and Johns Hopkins University Institutional Review Boards.

2.2 Blood pressure/hypertension

SBP and DBP were measured using a mercury manometer and a WelchAllyn adult one-tube one-piece blood pressure cuff. For each participant, two blood pressure measurements were taken by a trained research assistant, after the participant was seated for at least 15 minutes and before any other study procedures. The averages of the measurements were recorded. Additionally, the questionnaires completed by each woman included specific questions about whether they had been diagnosed with hypertension and if they were taking any medications, including anti-hypertensive medications. A woman was categorized as having hypertension if she had a DBP ≥ 90 mmHg and/or a SBP ≥ 140 mmHg and/or was taking an anti-hypertensive medication [6,13].

2.3 Genotyping

Genomic DNA was isolated from whole blood using the GenElute Blood Genomic DNA kit (Sigma, St. Louis, MO). Detection of the *CYP19A1* polymorphism (rs700518) was carried out using published methods[14,15]. The following primers were used: forward 5'-AGTAACACAGAACAGTTGCA-3' and reverse 5'-TCCAGACTCGCATGAATTCTCCGTA-3'. The polymerase chain reaction products were enzymatically digested (RsaI), and visualized by agarose gel electrophoresis. Specifically, one band at 188 base pairs was an indication that a subject was carrying the AA genotype. One band at 188 base pairs and one band at 164 base pairs indicated the participant was heterozygous (AG). One band located at 164 base pairs indicated the participant was homozygous for the G allele (GG)[14,15]. For statistical analyses, the genotypes were categorized as homozygous for the A allele (AA), heterozygous (AG), or homozygous for the G allele (GG). The group of women who were homozygous for the A allele (AA) served as the reference group.

2.4 Estradiol Assays

All assays were performed as previously described [14]. Briefly, serum concentrations of 17 β -estradiol were measured using enzyme-linked immunosorbent assay kits (ELISA) from Diagnostic Systems Laboratories, Inc. (Webster, TX). The assays were run using the manufacturers' instructions [18]. All assays were conducted in the same laboratory by a single investigator. All samples were run in duplicate and mean values for each participant were used in the analyses. The laboratory personnel were blind with respect to any information concerning study subjects. In addition, positive controls containing known amounts of estradiol were included in each batch. Further, some samples were run in multiple assays to ensure that the assay values did not dramatically shift over time. The minimum detection limit was 7pg/ml. Further, the intra-assay and inter-assay coefficients of variation were less than 5%. All samples were above the limit of detection.

2.5 Statistical analyses

Women were excluded from the analyses if they were missing data on race ($n = 2$), blood pressure ($n = 3$), or *CYP19A1* genotype ($n = 6$). Further, 11 women who reported being a race other than Caucasian or African American were excluded. One participant had missing SBP and DBP values, but reported using anti-hypertensive medications; this participant was not excluded from the analyses.

The unadjusted associations between 1) genotype and the blood pressure variables (DBP and SBP as continuous variables and hypertension as a categorical variable) and 2) genotype and the potential confounders [e.g. BMI, race, smoking] were examined using Chi-square tests for categorical variables and generalized linear models for continuous variables. In adjusted analyses, factors were considered to be potential effect modifiers or confounders if they were associated ($p < 0.1$) with genotype or were identified as being associated with high blood pressure or hypertension in the published literature. Effect modification was examined by stratifying the analyses by categories of each identified potential effect modifier (race, body mass index, age, cigarette smoking, and physical activity). To note, no effect modification was observed. Confounder-adjusted analyses were conducted using logistic regression for the hypertension variable and linear regression for the SBP and DBP variables.

Given the distribution of *CYP19A1* genotypes and standard deviations of SBP and DBP in the sample, the study had 80% power to detect differences in mean SBP and DBP of 4.5 mmHg and 3 mmHg, respectively, among women having at least one G allele compared to those who were homozygous for the A allele. Power calculations were based on a two-sided t-test and an $\alpha = 0.05$. Analyses were performed using SAS Version 9.1 (Cary, NC). A *P*-value of less than 0.05 was considered to be statistically significant.

2.6 Confounders

Data on a number of potential confounders were collected as part of the questionnaire and categorized as follows. Age and race were self-reported. Smoking status at the time of enrollment was determined using the questions "Have you ever smoked cigarettes?" and "Do you still smoke cigarettes?" Based on the participant's responses to these questions, she was categorized as a current, former, or never smoker. BMI was calculated based on height and weight measurements of the participant at the clinic visit. Usual physical activity was categorized as inactive/light and moderate/heavy using participant responses to questions regarding usual physical activity performed at work, home, and leisure during the last 12 months. For each area (work, home, and leisure), a participant was asked to think about the things she usually did during the last 12 months and to describe the kind of physical activity she performed. Possible responses were: inactive, light, moderate, and heavy. Menopausal

status was assigned as pre- or peri-menopausal. Pre-menopausal women were those who reported experiencing their last menstrual period within the past 3 months and experiencing 11 or more periods within the past year. Peri-menopausal women were those who reported experiencing: (1) their last menstrual period within the past year, but not within the past 3 months; or (2) their last menstrual period within the past 3 months and experiencing 10 or fewer periods within the past year. The number of live births was also self-reported and was grouped by the values of “1”, “2”, or “3 or more.”

3. Results

The general characteristics of the study sample (n=617) are presented in Table 1. The majority of the participants were 45 to 49 years old (64.2%; Table 1), Caucasian (84.9%; Table 1), and had a BMI <25.0 kg/m² (42.9%; Table 1). A small percent of women (9%; Table 1) reported that they were current smokers and 51.7% reported never smoking cigarettes (Table 1). Additionally, the majority of the women did not take anti-hypertensive medications (87.7%; Table 1) and were not categorized as hypertensive (78.6%; Table 1).

Most of the women in the study carried at least one copy of the minor allele G (AG 48.5%; GG 20.5%; Table 1). The allele frequency distribution followed the Hardy-Weinberg distribution ($\chi^2=0.25$) [16]. The distribution of the genotypes differed significantly by race, BMI, hypertension and SBP values. Specifically, a higher percentage of African American women (59.1%; Table 2) were homozygous for the A allele in comparison to Caucasian women (26.0%; Table 2). The association between BMI and genotype was of borderline statistical significance ($p = 0.05$; Table 2), with 39.6% of the obese women homozygous for the A allele (Table 2) compared to women in the other BMI categories (overweight: 26.6% and normal weight: 27.5%; Table 2). Additionally, the allele frequency of the major allele (A) was higher among women who were categorized as hypertensive (compared to non-hypertensive women (Table 2). Further, within the subgroup of women not taking anti-hypertensive medications, the mean SBP was significantly higher (117.0 mmHg; Table 2) for women who were homozygous for the A allele when compared to women who were heterozygous (AG) or homozygous for the G allele (113.6 mmHg and 112.5 mmHg, respectively; Table 2). In addition, the DBP values were of borderline statistical significance between by genotype ($p = 0.07$; Table 2). Lastly, estradiol levels were not significantly different by genotype (Table 2).

The unadjusted and adjusted associations between the *CYP19A1* SNP and hypertension are shown in Table 3. The unadjusted results showed that, in comparison with the AA genotype, women carrying the GG genotype were 42% less likely be hypertensive. After adjustment for potential confounders, the association between the selected SNP and hypertension was attenuated and not statistically significant. However, in the adjusted analyses, the odds of hypertension were significantly higher among women of African-American race (OR 3.17; 95% CI 1.87, 5.39), women with a higher BMI (25.0–29.9 kg/m²: OR 1.93; 95% CI 3.49; >30 kg/m²: OR 5.58; 95% CI 3.24, 9.59), and women of older age (OR 1.72; 95% CI 1.11, 2.67) compared to their counterparts.

The associations between the *CYP19A1* SNP, SBP, and DBP among women who reported not taking an anti-hypertensive medication are shown in Table 4. In the unadjusted analyses, women with the GG genotype had significantly lower mean SBP and DBP than women with the AA genotype. After adjustment for other risk factors, these associations were no longer statistically significant. In contrast, in the adjusted models, African-American race and higher BMI were significantly and positively associated with both SBP and DBP.

4. Discussion

In this study, while we observed that the genotype distribution was significantly different among women with and without hypertension, this difference was no longer statistically significant when the analyses were adjusted for potential confounders such as race and BMI. These findings suggest that race or factors other than the *CYP11A1* polymorphism investigated here may have a greater role in the development of hypertension among midlife women. Our data differ from those presented by Shimodaria et al;[1]. In their study, SBP levels were higher in women who carried the major allele A (i.e. AA or AG) than in women who were homozygous for the G allele. The reasons for the differences in our results compared to those of Shimodaria et al [1] are unknown, but could stem from differences in the study populations.

The potential confounding effects of age and BMI are consistent with other published studies [5,6]. In our study, women who had a BMI of 25 or greater or who were older (50 years of age or greater) had a significantly higher risk of hypertension compared to women who had a normal BMI ($<25 \text{ kg/m}^2$) or who were younger (<50 years of age), respectively. These findings are consistent with other studies that have directly examined the direct connections between hypertension and age or BMI and their potential mechanisms and roles in hypertension [5,6].

Further, the results of our study pertaining to race are consistent with the high prevalence of hypertension in African Americans observed in other studies[17–20]. In our analyses, African American women had about a 3-fold higher risk for hypertension compared to Caucasian women. In a previously published study, we reported statistically significant differences in certain characteristics such as smoking, BMI, and estradiol concentrations between the Caucasian and African American women in the study sample [21] that may explain their higher risk of hypertension. However, after adjustment for these factors, the risk estimates for hypertension and high blood pressure remained statistically significant. These findings implicate other factors not measured in this study that explain the association between race and hypertension in midlife women.

Our study had certain strengths contributing to the relevance of the results to the study of hypertension and potential effects of a genetic polymorphism in the aromatase gene. Specifically, we examined a novel association between a selected synonymous SNP (rs700518) in the *CYP19A1* gene and hypertension in a sample of women. In addition, we statistically analyzed the data while taking into account several potential confounders including menopausal status, race, BMI and age. Further, the blood pressure value that was used for the analyses is based on the average of two measurements at a single clinic visit and the trained clinic personnel made efforts to avoid any potential stressors that may lead to measurement error. For example, participants were asked to be seated for at least 15 minutes with legs uncrossed prior to the blood pressure measurement and the same arm was used for all readings for all patients. In addition, the allele distribution by race in this study is fairly consistent with the published data in the SNP data base of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs700518). Nonetheless, some limitations should be noted. Women did not have blood drawn on the same day of their menstrual cycle, and this may affect our estradiol measurements in the sample. Lastly, it is important to mention that the relatively small number of African-Americans in the sample ($n=93$) may have limited the statistical power among that group to see statistically significant differences.

In conclusion, estrogens have a significant role in the cardiovascular system through multiple systems in the body (e.g. vasodilator pathway, sodium and water balance)[4]. Due to the major physiological role estrogen has in the body, we hypothesized that a genetic polymorphism (rs700518) in *CYP19A1*, a gene that encodes aromatase, the enzyme responsible for converting androgens to estrogens, is associated with hypertension. Though we found a significant association between the selected polymorphism and hypertension, it was due to differences in the genotype by other factors such as race, as a statistically significant association between carriers of the G allele and hypertension was not observed in confounder-adjusted analysis. While factors such as race and BMI may play a role in hypertension, further studies should be conducted to determine whether other genetic polymorphisms in aromatase (e.g. a SNP in a nearby regulatory region which may segregate together with our selected SNP and jointly contribute to hypertension) or other SNPs in genes encoding steroidogenic enzymes are associated with hypertension as single factors or in multi-factorial analyses. Significant results may serve as a powerful tool in defining the pathogenesis of hypertension, and potentially lead to development of preclinical diagnostic tools along with customized treatment.

Acknowledgments

Source of funding: This work was supported by the National Institute on Aging (AG18400).

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Table 1

Study sample characteristics

Variable	n (%)
<u>Total sample size (n)</u>	617
<u>Age group</u>	
45 to 49	396 (64.2)
50 to 54	221 (35.8)
<u>Race</u>	
Caucasian	524 (84.9)
African American	93 (15.1)
<u>Body mass index (kg/m²)</u>	
Normal weight <25.0	265 (42.9)
Overweight 25.0 to 29.9	169 (27.3)
Obese >30.0	182 (29.5)
Missing	1 (0.2)
<u>Cigarette smoking status</u>	
Current smokers	56 (9.0)
Former smokers	241 (39.1)
Never smoke	319 (51.7)
Missing	1 (0.2)
<u>Taking anti-hypertensive medications</u>	
Yes	76 (12.3)
No	541 (87.7)
<u>Hypertension^a</u>	
Yes	132 (21.4)
No	485 (78.6)
<u>Mean blood pressure (mmHg) - all</u>	<u>mean, SD</u>
Systolic blood pressure (SBP)	116.1 (15.9)
Diastolic blood pressure (DBP)	74.0 (10.1)
<u>Mean blood pressure (mmHg) - no anti-hypertensive medications</u>	
SBP	114.4 (14.7)
DBP	73.2 (9.6)
<u>CYP19A1 (rs700518) polymorphism</u>	
^b AA	191 (31.0)
^c AG	299 (48.5)
^d GG	127 (20.5)

^a SBP ≥ 140 mmHg OR DBP ≥ 90 mmHg OR taking an antihypertensive medication

^b AA: homozygous for the A allele

^c AG: heterozygous

^d GG: homozygous for the G allele

Table 2

Study sample characteristics by *CYP19A1* (rs700518) genotype

	Sample <i>a</i> AA		<i>b</i> AG		<i>c</i> GG		P value
	n	n	%	n	%	n	
Age group							
45 to 49	396	123	31.1	186	47.0	87	0.46
50 to 54	221	68	30.8	113	51.1	40	22.0
							18.1
Race							
Caucasian	524	136	26.0	265	50.6	123	23.5
African-American	93	55	59.1	34	36.6	4	4.3
Body mass index (kg/m ²)							
<25.0	265	73	27.5	134	50.6	58	21.9
25.0 to 29.9	169	45	26.6	88	52.1	36	21.3
>30.0	182	72	39.6	77	42.3	33	18.1
missing	1						
Smoking status							
Current	56	21	37.5	25	44.6	10	17.9
Former	241	80	33.2	111	46.1	50	20.7
Never	319	89	27.9	163	51.1	67	21.0
Missing	1						
Menopausal status							
Pre-menopausal	232	72	31.0	107	46.1	53	22.8
Peri-menopausal	374	116	31.0	187	50.0	71	19.0
Missing	11						
Number of live births							
None	143	42	29.4	73	51.0	28	19.6
1	108	337	34.3	45	41.7	26	24.1
2	229	70	30.6	110	48.0	49	21.4
3 or more	137	42	30.7	71	51.8	24	17.5

	Sample		^a AA		^b AG		^c GG		P value	
	n	n	n	%	n	%	n	%	%	
Physical activity										
None/light	368	115	31.3	179	48.6	74	20.1			0.94
Moderate/heavy	249	76	30.5	120	48.2	53	21.3			
^dHypertension										
Yes	132	53	40.2	56	42.4	23	17.4			0.04
No	493	138	28.8	243	49.3	104	21.1			
Anti-hypertensive medications										
Yes	76	28	36.8	34	44.7	14	18.4			0.49
No	541	163	30.1	265	49.0	113	20.9			
^eSBP										
no medications (mean, mmHg)	541	117 (114.8, 119.3)	113.6 (111.8, 115.4)	112.5 (109.8, 115.2)						0.02
^fDBP										
no medications (mean mmHg)	541	74.4 (72.9, 75.9)	73.0 (71.9, 74.2)	71.7 (70.0, 73.5)						0.07
Estradiol (geometric mean, 95% CI)	617	92.0 (81.6, 103.3)	96.8 (88.3, 106.2)	111.7 (96.9, 128.7)						0.11

^a AA: homozygous for the A allele

^b AG: heterozygous

^c GG: homozygous for the G allele

^d SBP $\geq$ 140 mmHg OR DBP $\geq$ 90 mmHg OR taking an antihypertensive medication

^e SBP: systolic blood pressure

^f DBP: diastolic blood pressure

Table 3

Unadjusted and adjusted odds ratios (OR) and confidence intervals (95% CI) for the association between *CYP19A1* (rs700518) polymorphism and blood pressure

Variable	Unadjusted model		^f Adjusted model	
	^d OR	^e 95% CI	OR	95% CI
<i>CYP19A1</i>(rs700518)				
^a AA	1.00	(reference)	1.00	(reference)
^b AG	0.60	(0.39, 0.92)	0.85	(0.52, 1.39)
^c GG	0.58	(0.33, 0.99)	0.95	(0.51, 1.80)
Race				
Caucasian			1.00	(reference)
African-American			3.17	(1.87, 5.39)
Body mass index (kg/m²)				
<25.0			1.00	(reference)
25.0–29.9			1.93	(1.06, 3.49)
>30.0			5.58	(3.24, 9.59)
Age				
45–49			1.00	(reference)
50–54			1.72	(1.11, 2.67)
Cigarette smoking				
Never			1.00	(reference)
Former			1.65	(0.41, 1.05)
Current			1.38	(0.69, 2.76)
Physical activity				
None/light			1.00	(reference)
Moderate/severe			0.78	(0.49, 1.23)

^a AA: homozygous for the A allele

^b AG: heterozygous

^c GG: homozygous for the G allele

^d odds ratio

^e 95% confidence interval

^f adjusted for other variables on the table

Unadjusted and adjusted associations between *CYP19A1* (rs700518) polymorphism and SBP and DBP among women not taking antihypertensive medication

Table 4

Variable	SBP Unadjusted model		^d Adjusted model		DBP Unadjusted model		^d Adjusted model	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
<i>CYP19A1</i> (rs700518)								
^a AA	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
^b AG	-3.40	(-6.27, -0.54)	-0.93	(-3.60, 1.75)	-1.42	(-3.30, 0.46)	0.00	(-1.80, 1.80)
^c GG	-4.55	(-8.07, -1.03)	-1.49	(-4.79, 1.81)	-2.70	(-5.02, -0.39)	-0.92	(-3.14, 1.30)
Race								
Caucasian			1.00	(reference)			1.00	(reference)
African-American			6.64	(2.98, 10.31)			3.90	(1.44, 6.36)
Body mass index (kg/m²)								
<25.0			1.00	(reference)			1.00	(reference)
25.0-29.9			4.68	(1.99, 7.36)			3.36	(1.56, 5.17)
>30.0			13.62	(10.67, 16.57)			8.02	(6.03, 10.01)
Age								
45-49			1.00	(reference)			1.00	(reference)
50-54			0.80	(-1.58, 3.17)			0.30	(-1.30, 1.90)
Cigarette smoking								
Never			1.00	(reference)			1.00	(reference)
Former			-0.92	(-3.28, 1.44)			-1.08	(-2.67, 0.51)
Current			1.34	(-2.92, 5.60)			0.40	(-2.47, 3.26)
Physical activity								
None/light			1.00	(reference)			1.00	(reference)
Moderate/severe			-0.92	(-3.26, 1.41)			-0.69	(-2.26, 0.89)

^a AA: homozygous for the A allele

^b AG: heterozygous

^c GG: homozygous for the G allele
^d Adjusted for other variables presented on the table