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Vitamin D Metabolism-Related Gene Haplotypes and Their Association with Metabolic Disturbances Among African-American Urban Adults

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May A. Beydoun[1], Sharmin Hossain[1], Salman M. Tajuddin[1], Jose A. Canas[2], Marie Kuczmarski[3], Hind A. Beydoun[4], Michele K. Evans[1] & Alan B. Zonderman[1]

Epidemiological studies have confirmed associations of the vitamin D receptor (*VDR*) and vitamin D-related gene polymorphisms with adiposity and other metabolic disturbances. Those associations may be sex-specific. We evaluated the cross-sectional and longitudinal relationships between metabolic disturbances and haplotypes constructed from single nucleotide polymorphisms of *VDR* (BsmI:G/A: rs1544410; ApaI:A/C: rs7975232; and TaqI:G/A: rs731236) and *MEGALIN* (rs3755166:G/A; rs2075252:C/T and rs2228171:C/T) genes, in a sample of African-American adults. From 1,024 African Americans participating in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS, 2004–2013, Baltimore, MD), our analyses included 539 participants with complete genetic, baseline covariate and metabolic outcome data (at baseline and follow-up). Mean ± SD period of follow-up was 4.64 ± 0.93 y. Multivariable-adjusted Cox proportional hazards and logistic regression models were conducted. Among key findings, in men, incident hypertension was inversely related to $MEGALIN_1$ (GCC), [HR = 0.45, 95% CI: 0.23–0.90, p = 0.024]. Overall, there was a direct, linear dose-response association between VDR_2 (AAG: BAt) and MetS at baseline [OR = 1.60, 95% CI: 1.11–2.31, p = 0.012], while among men, VDR_3 (GAA: bAT) was inversely related to baseline MetS [OR = 0.40, 95% CI: 0.19–0.81, p = 0.011]. In conclusion, *VDR* and *MEGALIN* gene variations can affect prevalent MetS and the incidence rate of hypertension, respectively, among African-American urban adults.

The metabolic syndrome (MetS), is a condition that often clusters together central obesity, elevated blood pressure, lower HDL cholesterol, hypertriglyceridemia and hyperglycemia[1]. MetS increases type 2 diabetes risk and that of cardiovascular disease by 5-folds and 1.7-folds, respectively[2,3]. MetS is heritable and polygenic[4]. Genetics contributes to 16%-85% of Body Mass Index (BMI) variability[5] and 37%-81% in that of waist circumference (WC) (e.g[6].). MetS is an important public health threat triggering higher disability, health care costs and mortality from all causes[7–9].

Moreover, obesity may be directly involved in the etiology of vitamin D deficiency, with prior evidence of an inverse relationship between serum 25-hydroxyvitamin D [25(OH)D] concentration and various measures of adiposity[10]. Conversely, vitamin D3 may influence obesity risk by modulating intracellular calcium homeostasis, due to the fact that higher intracellular calcium triggers lipogenesis and suppresses lipolysis[11]. Many organs express vitamin D receptor (VDR), a component the super-family termed "nuclear hormone receptor". The complex made of VDR and $1,25(OH)_2D_3$ modulates transcription of vitamin D responsive genes[12] and influences

[1]Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIA/NIH/IRP, Baltimore, MD, United States. [2]Pediatric Endocrinology, Nemours Children's Clinic, Jacksonville, FL, United States. [3]Department of Behavioral Health and Nutrition, University of Delaware, Newark, DE, United States. [4]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, United States. Michele K. Evans and Alan B. Zonderman jointly supervised this work. Correspondence and requests for materials should be addressed to M.A.B. (email: baydounm@mail.nih.gov)

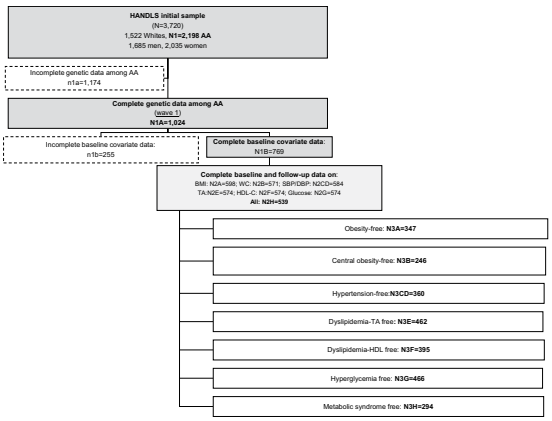

Figure 1. Participant Flow Chart.

adipocyte differentiation[13]. The effect of *VDR* gene polymorphism can potentially be sex-specific as shown in at least one previous study with adiposity phenotypes[14].

Epidemiological studies have confirmed associations of *VDR* polymorphisms with adiposity and other metabolic disturbances[6,14–23]. However, studies specifically examining adiposity outcomes either had small sample sizes (<400), (e.g[15,16,24].) or were restricted to one sex, (e.g.[6,16].) but more importantly were all cross-sectional or case-control by design and none to date have examined these associations among African-American adults.

MEGALIN (aka low-density lipoprotein receptor-related protein-2 [LRP-2]), is the endocytic vitamin D-binding protein receptor which allows vitamin D entry into cells and whose expression is directly regulated by both vitamin D[25]) and vitamin A[26]. MEGALIN may influence obesity by mediating the transport of leptin through the blood-brain barrier and modulating its signaling of both leptin and thyroid hormones[27] Collectively, leptin and thyroid hormones affect adiposity through energy metabolism regulation[28]. MEGALIN acting also as the receptor for sex-hormone binding globulin (*SHBG*), is involved in interactions between estrogen, vitamin D and intracellular calcium within adipocytes, leading to a potentially sex-specific effect of *MEGALIN* polymorphisms on various phenotypes of obesity, as indicated by findings from previous studies[14,29]

In this study conducted, we hypothesize that selected *VDR* and *MEGALIN* gene polymorphisms have sex-specific associations with several key metabolic disturbances in a longitudinal study of African-American urban adults.

Subjects and Methods

Database. The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is a prospective cohort study, initiated in 2004. It recruited an area probability sample of African Americans and whites residing in 13 neighborhoods of Baltimore, Maryland and aged 30–64 years at baseline. In the baseline visit (visit 1: 2004–2009), screening, followed by recruitment and household interviews were completed during phase 1, while phase 2 consisted of in-depth examinations in a mobile Medical Research Vehicles (MRV)[30]. Phase 1 of visit 1 included a general household questionnaire and 1 24 hr dietary recall, while phase 2 of that visit collected more in-depth psychosocial data, anthropometric, physiologic and body composition measurements, a fasting blood draw, as well as a second 24 hr dietary recall. The first follow-up visit (visit 2), initiated in 2009, collected similar data as in phase 2 of visit 1 through 2013, with few variations and followed a similar protocol. In both visits, participants provided informed consent form after reviewing a protocol booklet and a video that explained study procedures including future contact efforts. The National Institute on Environmental Health Sciences Institutional Review Board of the National Institutes of Health approved the HANDLS protocol and all methods were performed in accordance with the relevant guidelines and regulations. Participants are remunerated. In this study, we analyzed longitudinal HANDLS data from initial and first follow-up examinations among a sample of African-Americans participating in the HANDLS study, who had complete genetic data. Time elapsed between examination visit 1 (Wave 1:2004–2009) and visit 2 (also known as Wave 3:2009–2013[31]), ranged between <1 y and ~8 y, with a mean of 4.64 ± 0.93 y.

Study subjects. Of the 3,720 baseline participants (mean ± SD age(y) of 48.3 ± 9.4, 45.3% men, and 59.1% African-American), data on genetic polymorphisms were complete for 1,024 participants self-reporting to be African American. However, missing data on covariates reduced our sample to n = 769, and further exclusions resulted in a sample size range of 574 to 598, with 539 participants having complete data on relevant baseline and follow-up outcome measurements (cross-sectional part of the analysis). In the longitudinal part of our analyses, participants who were initially free from metabolic disturbances were selected for each outcome. Their sample sizes ranged from n = 246 (central obesity-free) to n = 466 (hyperglycemia-free) and those who were MetS-free consisted of n = 294 baseline participants (Fig. 1).

Anthropometric measures and metabolic outcome variables. BMI, measured as weight/height^2, kg/m^2 was computed for each participant based on measured weight and height. Furthermore, WC (in cm.) was measured using a tape that was wrapped around the waist near the navel, starting from the hip bone. Systolic and

diastolic blood pressures (SBP and DBP) were measured by averaging 1 right and 1 left sitting non-invasive assessments using brachial artery auscultation using a stethoscope, an aneroid manometer, and an inflatable cuff. After an overnight fast (8–12 hours), a blood draw was taken from an antecubital vein. From this blood draw, fasting glucose (FG), triacylglycerols (TAG), total cholesterol, and HDL-C were assessed using a spectrophotometer (Olympus 5400; Quest Diagnostics).

Classification of health outcomes. General obesity was defined as BMI $\geq$30 kg/m^2, while central obesity (aka abdominal obesity) was based on WC $\geq$102 cm or 40 inches in men and $\geq$88 cm or 35 inches in women[32]. Participants who screened positive on at least 3 of 5 conditions ((1) central obesity (see above); (2) blood pressure $\geq$130/85 mmHg; (3) dyslipidemia: TAG $\geq$1.695 mmol/L (150 mg/dl); (4) dyslipidemia: HDL-C $<$ 40 mg/dL in men or $<$50 mg/dL in women; (5) fasting plasma glucose $\geq$6.1 mmol/L (110 mg/dl)[33].) were classified as MetS-positive[1] We examined binary prevalent (V1 and V2) and incident outcomes, namely obesity, central obesity, MetS and its remaining individual components (i.e. hypertension, dyslipidemia-TA, dyslipidemia-HDL and hyperglycemia).

Vitamin D receptor and MEGALIN (LRP2) SNP and SNPHAP. Study participants were genotyped to 907,763 single nucleotide polymorphisms (SNPs) using the Illumina 1 M and 1M-Duo genotyping arrays. Details regarding genotype quality control criteria are provided in Supplemental Methods 1.

For the present study, in the main analysis, we selected *VDR* and *MEGALIN* SNPs based on previously published validation studies of adiposity or various health outcomes that were linked to adiposity[6,15–18] and a replication study of similar outcomes among European ancestry participants from the Baltimore Longitudinal Study of Aging (BLSA)[14]. Three *VDR* SNPs:; rs1544410 (BsmI: G/A); rs7975232 (ApaI: A/C) and rs731236 (TaqI: G/A), and three *MEGALIN* SNPs (rs3755166: G/A; rs2075252: C/T; rs2228171: C/T) were chosen for haplotype analysis. The final selected SNPs and their frequencies were published elsewhere[34].

VDR and *MEGALIN* SNPs haplotypes (SNPHAP) were considered main predictors in our analysis. For *VDR* gene, the BsmI, ApaI and TaqI SNP were combined together to construct SNPHAP, as was done in a previous study[34], and their haplotype frequencies in the population were comparable to at least one other study conducted among Whites[35]. Four SNPHAP were detected in our sample with the SNP combinations being either one of the three: VDR_1: GCA [baT], VDR_2: AAG [BAt], VDR_3: GAA [bAT] and VDR_4: AAA [BAT] for one or two alleles. Participants were coded as 0 = having no VDR_x haplotype; 1 = having one allele carrying the VDR_x haplotype; 2 = having two alleles with the VDR_x haplotype. This approach was similarly applied to the three *MEGALIN* SNP and eight haplotypes were found. However, only two haplotypes were extracted in the present analyses, given that their frequency was greater than 10%. The most common SNPHAP are comparable to our previous study[34]. Detailed descriptions the SNPHAP are found in Table 1. Furthermore, all available SNPs in and around the *VDR* and *MEGALIN* genes were also selected for a supplemental analysis, after passing through eligibility criteria related to reliability of imputation and minor allele frequency. Details on filtering of SNPs is further discussed in Supplemental Method 1–2. Outcomes of interest were MetS (incident, visits 1 and 2).

Covariates. Our analyses included the following covariates: baseline age, sex, poverty status, education, smoking, drug use and self-rated health, among fixed or baseline variables. The Healthy Eating Index (HEI-2010) total score, computed using two 24-hr recalls administered at the initial visit, reflected overall dietary quality (see http://appliedresearch.cancer.gov/tools/hei/tools.html) or http://handls.nih.gov/06Coll-dataDoc.htm) and was included in our analyses. Similarly, total energy intake (kcal/d) was included in our models as a potential confounder based on the average of initial 2 24-hr dietary recalls. Finally, 10 principal components were included in order to control for any residual effects of population structure (Supplemental method 1). Covariates were selected based on their known association with the metabolic outcomes of interest. Due to the limited sample size, a sensitivity analysis was conducted for parts of the analysis adjusting only for basic socio-demographic factors, namely age, sex, poverty status and education, as well as the inverse mills ratio.

Statistical analysis. The main part of the analysis was conducted using Stata release 15.0[36]. For each SNP, the Hardy-Weinberg equilibrium assumption was tested using exact test, and pair-wise linkage disequilibrium (LD) was computed and visualized using Haploview version 4.2 package[37]. To describe study participant characteristics and compare them by sex, *t*-test and χ^2 test were used for continuous and categorical variables, respectively.

Both cross-sectional and longitudinal relationships of *VDR* and *MEGALIN* SNPHAP with binary metabolic outcomes, including obesity, central obesity and the MetS were examined. To test cross-sectional associations, multi-variable logistic regression models were conducted for each outcome, controlling for baseline age, sex, poverty status, education, first-visit current smoking and drug use, self-reported health and the HEI-2010 total score, the 10 principal components to adjust for population structure and the inverse mills ratio. For longitudinal analyses, we defined time-to-event from baseline visit (i.e. delayed entry) until outcome or censoring at second visit and constructed multiple Cox proportional hazards models for incident metabolic outcome, overall and after stratifying by sex. Follow-up time was expressed in years. In addition to examining obesity (BMI and WC-based) and MetS as incident outcomes, other components of the MetS were also evaluated as individual incident metabolic outcomes. Linear trend test for associations between haplotype dosage (0, 1, 2 copies) and metabolic outcomes was performed.

Furthermore, selection bias due to the non-random selection of participants with genetic data from target population, was corrected at least in part using a 2-stage Heckman selection model[38]. At first stage, probit models were constructed to calculate an inverse mills ratio, a function of the predicted selection probability, conditional on key covariates, as previously described[39]. At a second stage, the inverse mills ratio was entered into the

	SNP Haplotypes (SNPHAP)	
	Definitions	**Distributions, %**
VDR	[BsMI/ApaI/TaqI]	
Overall	VDR_1: GCA [baT]	36.5
	VDR_2: AAG [BAt]	19.1
	VDR_3: GAA [bAT]	25.2
	VDR_4: AAA [BAT]	10.1
Allelic copies		
VDR_1	VDR_1: GCA	
0		68.0
1		18.5
2		13.6
VDR_2	VDR_2: AAG	
0		78.5
1		17.3
2		4.2
VDR_3	VDR_3: GAA	
0		27.3
1		65.8
2		6.8
VDR_4	VDR_4: AAA	
0		90.2
1		8.8
2		1.0
MEGALIN	[rs3755166/rs2075252/rs2228171]	
Overall		
	$MEGALIN_1$:GCC	53.3
	$MEGALIN_2$:ACC	24.3
Allelic copies		
$MEGALIN_1$	$MEGALIN_1$:GCC	
0		10.1
1		63.5
2		26.5
$MEGALIN_2$	$MEGALIN_2$:ACC	
0		64.9
1		30.8
2		4.3

Table 1. Findings from haplotype analysis: definitions and distributions of SNPHAP for the selected *VDR* and *LRP2* (*MEGALIN*) SNPs, $n = 1{,}024$[1]. *Abbreviations*: SNP = Single Nucleotide Polymorphism; SNPHAP = Single Nucleotide Polymorphism Haplotype; *VDR* = Vitamin D receptor gene. [1]SNPHAP were defined based on three *VDR* SNP combinations: BsmI, ApaI and TaqI and were expressed as dosage (0 = none, 1 = one copy, 2 = 2 copies) in the main analysis. SNPHAP were defined based on all three *MEGALIN* SNP combinations rs3755166/rs2075252/rs2228171 and were expressed as dosage (0 = none, 1 = one copy, 2 = 2 copies) in the main analysis.

multi-variable logistic or Cox PH models, thus adjusting for selection bias. Stratification was done and effect modification was tested (by adding 2-way interaction terms) by sex for all analyses, including supplemental analyses for single SNPs in and around the *VDR* and *MEGALIN* genes. Gender difference in the relationship between *MEGALIN* gene polymorphisms and metabolic outcomes was an a priori hypothesis[40].

Finally, in all our analyses, type I error was set 0.05 prior to correction for multiple testing. A p-value <0.10 was considered as marginally significant. Correction for multiple testing was conducted using a familywise Bonferroni process in which a family was defined by the metabolic outcome and the gene[41]. Thus, the critical p-value was reduced to $0.05/4 = 0.0125$ in the case *VDR* SNPHAP associations, whereas for *MEGALIN* SNPHAPs it was reduced to $0.05/2 = 0.025$. Correction for multiple testing followed a similar though less stringent approach, whereby a critical p-value per outcome of interest was reduced to 0.01 for overall analysis and 0.02 for sex-specific analysis. For 2-way interaction terms, particularly for testing effect modification by gender, type I error was kept at 0.05 due to reduced statistical power[42].

Results

All examined SNPs exhibited Hardy-Weinberg equilibrium ($P > 0.002$). Variants within each *VDR* and *MEGALIN* (*LRP2*) gene were deemed in low linkage equilibrium ($r^2 < 0.30$). The four selected *VDR* haplotypes had an

	All		Men		Women	
	(*n* = 539)		(*n* = 230)		(*n* = 309)	
	Mean, %	SE	Mean, %	SE	Mean, %	SE
Socio-demographic and health characteristics, V1						
Age (y)	48.6	0.4	49.0	0.6	48.3	0.5
Men (%)	42.7		—		—	
Above poverty (%)	52.5		54.8		50.8	
Education (%)						
<High School	3.9		4.3		3.6	
High School	61.2		59.6		62.5	
>High School	34.9		36.1		34.0	
Self-rated health (%)						
Poor/fair	21.3		20.0		22.3	
Good	44.3		45.2		43.7	
Very good/excellent	34.3		34.8		34.0	
Current smoker, yes (%)	45.3		51.3[2]		40.8	
Current smoker, missing (%)	5.0		3.9		5.8	
Current illicit drug user, yes (%)	18.6		23.9[2]		14.6	
Current illicit drug user, missing (%)	5.0		3.9		5.8	
Dietary intake and quality, V1						
Energy intake (kcal/d)	2,033	43	2408[2]	74	1755	45.4
HEI-2010	42.8	0.5	41.7[2]	0.7	43.7	0.6
Metabolic outcomes, V1, V2						
BMI (kg/m^2)						
V1	29.9	0.3	28.0[2]	0.4	31.3	0.5
V2	30.5	0.3	28.3[2]	0.4	32.2	0.5
Waist circumference (cm)						
V1	98.6	0.8	96.7[2]	1.1	100.1	1.1
V2	102.3	0.7	100.1[2]	1.0	103.9	1.1
SBP (mm Hg)						
V1	122.1	0.7	121.2	1.0	122.8	1.1
V2	124.8	0.8	123.0[2]	1.2	126.2	1.1
DBP (mm Hg)						
V1	73.2	0.5	74.0	0.7	72.6	0.6
V2	71.9	0.4	72.7	0.7	71.2	0.5
HDL-C (mg/dL)						
V1	55.0	0.7	51.5[2]	1.1	57.7	1.0
V2	59.1	0.8	54.7[2]	1.2	62.4	1.1
TA (mg/dL)						
V1	107.0	3.3	116.1[2]	6.5	100.2	2.9
V2	110.8	2.6	113.9	4.3	108.5	3.1
Fasting blood glucose (mg/dL)						
V1	104.1	1.7	108.5[2]	3.1	100.8	1.8
V2	103.2	1.5	107.1[2]	2.6	100.3	1.7
Metabolic disturbance, V1, V2, incident						
Obesity (%, BMI ≥ 30)						
V1	41.2		30.0[2]		49.5	
V2	46.8		33.9[2]		56.3	
Incident	15.0		11.5		18.5	
Central obesity (%)[3]						
V1	57.7		36.5[2]		73.5	
V2	66.4		43.0[2]		83.8	
Incident	31.7		21.7[2]		49.4	
MetS (%)[4,5]						
V1	24.9		22.2		26.9	
V2	22.8		18.7[2]		25.9	
Incident	12.2		9.8		14.3	

Table 2. Gender differences in baseline characteristics and time-dependent metabolic outcomes among African-Americans with complete genetic, time-dependent metabolic data and baseline covariate data: HANDLS 2004–2009 and 2009–2013[1]. [1]HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; SBP, systolic blood pressure; DBP, diastolic blood pressure; TA, triacylglycerols; MetS, metabolic syndrome, V1 = Visit 1, V2 = Visit 2. [2]$P < 0.05$ for testing the null hypothesis that means or proportions are the same between men and women. [3]Defined as waist circumference > 102 cm for men and > 88 cm for women. [4]Defined based on NCEP ATP III described in Methods. [5]Three or more metabolic disturbances as listed above represent MetS. Metabolic disturbances may range between 0 and 5.

	Incident metabolic disturbance								
	All			Men			Women		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Obesity: Models A-F	**(N = 347)**			**(N = 174)**			**(N = 173)**		
VDR_1: GCA (0,1,2)	1.30	(0.87;1.93)	0.20	1.19	(0.69;2.07)	0.54	1.19	(0.69;2.07)	0.54
VDR_2: AAG (0,1,2)	0.89	(0.48;1.63)	0.71	1.02	(0.35;2.94)	0.97	0.97	(0.35;2.64)	0.95
VDR_3: GAA (0,1,2)	1.21	(0.66;2.20)	0.55	1.21	(0.34;4.31)	0.76	1.49	(0.63;3.48)	0.36
VDR_4: AAA(0,1,2)	0.74	(0.27;2.03)	0.57	0.83	(0.14;4.91)	0.84	0.51	(0.11;2.45)	0.40
$MEGALIN_1$: GCC (0,1,2)	0.94	(0.55;1.61)	0.83	0.50	(0.17;1.48)	0.21	1.59	(0.74;3.42)	0.23
$MEGALIN_2$: ACC (0,1,2)	1.23	(0.72;2.10)	0.45	1.51	(0.58;3.96)	0.40	0.63	(0.36;1.50)	0.30
Central obesity: Models A-F	**(N = 246)**			**(N = 157)**			**(N = 89)**		
VDR_1: GCA (0,1,2)	1.19	(0.82;1.74)	0.37	1.00	(0.49;2.01)	1.00	***1.63***	***(0.96;2.76)***	***0.068***
VDR_2: AAG (0,1,2)	1.02	(0.62;1.70)	0.93	0.83	(0.41;1.71)	0.62	1.38	(0.68;3.63)	0.29
VDR_3: GAA (0,1,2)	0.81	(0.49;1.35)	0.42	1.60	(0.60;4.24)	0.35	**0.47**	**(0.23;0.95)**	**0.036**
VDR_4: AAA(0,1,2)	***1.57***	***(0.97;2.52)***	***0.064***	1.91	(0.78;4.66)	0.16	1.34	(0.58;3.09)	0.49
$MEGALIN_1$: GCC (0,1,2)	0.86	(0.56;1.31)	0.49	0.57	(0.27;1.20)	0.14	0.92	(0.48;1.73)	0.80
$MEGALIN_2$: ACC (0,1,2)	1.27	(0.81;1.98)	0.30	**2.16**	**(1.04;4.32)**	**0.040**	0.90	(0.45;1.82)	0.78
Hypertension: Models A-F	**(N = 360)**			**(N = 159)**			**(N = 201)**		
VDR_1: GCA (0,1,2)	1.08	(0.77;1.51)	0.67	0.88	(0.49;1.57)	0.66	1.45	(0.91;2.31)	0.12
VDR_2: AAG (0,1,2)	1.30	(0.86;1.97)	0.21	1.03	(0.50;2.13)	0.93	**1.98**	**(1.09;3.62)**	**0.026**
VDR_3: GAA (0,1,2)	1.00	(0.62;1.59)	0.99	1.45	(0.61;3.43)	0.40	0.59	(0.30;1.14)	0.12
VDR_4: AAA(0,1,2)	0.86	(0.46;1.62)	0.65	1.37	(0.54;3.49)	0.50	0.81	(0.30;2.15)	0.67
$MEGALIN_1$: GCC (0,1,2)	0.77	(0.52;1.12)	0.17	**0.45**	**(0.23;0.90)**	**0.024**	1.08	(0.59;1.96)	0.81
$MEGALIN_2$: ACC (0,1,2)	0.84	(0.57;1.22)	0.36	1.28	(0.70;2.36)	0.43	**0.55**	**(0.31;0.97)**	**0.039**
Dyslipidemia-TA: Models A-F	**(N = 462)**			**(N = 183)**			**(N = 279)**		
VDR_1: GCA (0,1,2)	***1.43***	***(0.95;2.16)***	***0.085***	1.37	(0.86;2.86)	0.14	1.42	(0.71;2.83)	0.33
VDR_2: AAG (0,1,2)	1.08	(0.67;1.76)	0.75	0.90	(0.37;2.23)	0.82	1.30	(0.62;2.70)	0.49
VDR_3: GAA (0,1,2)	0.82	(0.47;1.42)	0.47	0.58	(0.24;1.42)	0.23	0.87	(0.39;1.90)	0.72
VDR_4: AAA(0,1,2)	0.59	(0.23;1.56)	0.29	0.96	(0.24;3.79)	0.96	0.43	(0.09;2.02)	0.28
$MEGALIN_1$: GCC (0,1,2)	0.95	(0.59;1.53)	0.84	1.03	(0.46;2.29)	0.94	1.23	(0.58;2.58)	0.59
$MEGALIN_2$: ACC (0,1,2)	0.90	(0.55;1.47)	0.67	0.80	(0.31;2.06)	0.65	0.66	(0.83;1.32)	0.24
Dyslipidemia-HDL: Models A-F	**(N = 395)**			**(N = 184)**			**(N = 211)**		
VDR_1: GCA (0,1,2)	1.23	(0.68;2.19)	0.49	1.36	(0.48;3.81)	0.36	1.05	(0.30;3.65)	0.94
VDR_2: AAG (0,1,2)	0.37	(0.11;1.26)	0.11	0.66	(0.15;2.82)	0.57	0.17	(0.01;2.51)	0.20
VDR_3: GAA (0,1,2)	0.89	(0.40;2.01)	0.79	0.76	(0.18;3.27)	0.71	0.72	(0.16;3.16)	0.66
VDR_4: AAA(0,1,2)	1.24	(0.37;2.64)	0.59	0.50	(0.07;3.76)	0.50	2.47	(0.78;7.83)	0.12
$MEGALIN_1$: GCC (0,1,2)	0.70	(0.36;1.38)	0.30	0.81	(0.26;2.49)	0.71	0.73	(0.24;2.24)	0.58
$MEGALIN_2$: ACC (0,1,2)	1.67	(0.90;3.10)	0.11	2.34	(0.80;6.85)	0.12	1.30	(0.46;3.62)	0.63
Hyperglycemia: Models A-F	**(N = 466)**			**(N = 187)**			**(N = 279)**		
VDR_1: GCA (0,1,2)	***1.51***	(***0.99;2.29***)	***0.054***	**2.26**	**(1.11;4.62)**	**0.025**	1.08	(0.57;2.04)	0.80
VDR_2: AAG (0,1,2)	0.54	(0.25;1.14)	0.11	0.97	(0.34;2.77)	0.96	0.49	(0.16;1.45)	0.20
VDR_3: GAA (0,1,2)	0.88	(0.47;1.64)	0.69	0.67	(0.22;2.05)	0.49	0.89	(0.36;2.23)	0.81
VDR_4: AAA (0,1,2)	0.81	(0.35;1.88)	0.63	0.39	(0.04;3.69)	0.41	1.92	(0.65;5.68)	0.24
$MEGALIN_1$: GCC (0,1,2)	0.89	(0.51;1.53)	0.67	***0.40***	***(0.14;1.14)***	***0.087***	1.09	(0.52;2.28)	0.81
$MEGALIN_2$: ACC (0,1,2)	0.74	(0.41;1.33)	0.32	1.31[3]	(0.52;3.32)	0.57	**0.39**	**(0.16;0.97)**	**0.043**
Metabolic syndrome: Models A-F	**(N = 294)**			**(N = 133)**			**(N = 161)**		
VDR_1: GCA (0,1,2)	0.86	(0.44;1.66)	0.64	1.16	(0.37;3.65)	0.79	0.88	(0.33;2.39)	0.81
VDR_2: AAG (0,1,2)	0.89	(0.36;2.01)	0.78	0.92	(0.13;6.58)	0.93	1.02	(0.32;3.22)	0.97
VDR_3: GAA (0,1,2)	1.99	(0.87;4.53)	0.10	1.24	(0.19;8.02)	0.82	2.34	(0.66;8.30)	0.19
VDR_4: AAA(0,1,2)	***0.18***	***(0.02;1.27)***	***0.085***	2.42	(0.27;21.90)	0.43	__		
$MEGALIN_1$: GCC (0,1,2)	0.88	(0.46;1.70)	0.71	**0.08**	**(0.01;0.88)**	**0.039**	0.91	(0.30;2.72)	0.86
$MEGALIN_2$: ACC (0,1,2)	0.95	(0.50;1.81)	0.88	0.94	(0.19;4.69)	0.94	1.02	(0.37;2.81)	0.97

Table 3. *VDR* and *MEGALIN* SNP haplotype (SNPHAP) associations with incident metabolic disturbances: Cox proportional hazards models, ($n = 246$–466); HANDLS study. *Abbreviations*: BMI = body mass index (calculated as weight in kg/square of height in meters); SNP = Single Nucleotide polymorphism; SNPHAP = SNP haplotype; *VDR* = Vitamin D receptor gene; Note that VDR_1, VDR_2, VDR_3 denote *VDR* SNPHAP, whereas $MEGALIN_1$, $MEGALIN_2$ and $MEGALIN_3$ denote *MEGALIN* SNPHAP. *Note*: Shaded estimated indicate significance upon correction for multiple testing. Models A-F indicate that each haplotype was entered in a separate regression model to estimate its association with different metabolic outcomes. [1]See Table 1 for more details on definition the SNP haplotypes. (0,1,2) refers to ordinal coding with "0", "1" and "2" copies of each haplotype. Three *VDR* SNP were combined to form the haplotypes, namely BsmI, ApaI and TaqI. Only haplotypes 1 and 2 were selected for *MEGALIN* since their overall prevalence was > 10%. [2]Models were adjusted for age, sex, poverty status, education, current smoking status, current illicit drug use, self-rated health, total energy intake, HEI-2010 total score, 10 principal components for population structure, and the inverse mills ratio. [3]$P < 0.05$ for null hypothesis that sex × SNPHAP interaction term = 0 in a model where main effect of sex was added.

overall prevalence ranging from 10.1% for VDR_4 to 36.5% for VDR_1. A large proportion of African-Americans (65.8%) had 1 copy of VDR_3; only 1% had 2 copies of VDR_4. Similarly, among the selected *MEGALIN* haplotypes, $MEGALIN_1$: GCC was the most common (53.3%), with 63.5% having 1 copy and only 4.3% having 2 copies of $MEGALIN_2$: ACC (Table 1).

Table 2 presents baseline characteristics and time-dependent metabolic outcomes (Fig. 1: $n_{2h} = 539$). Most notably men had higher prevalence of smoking and drug use compared to women as well as higher energy intake, poorer overall dietary quality (HEI-2010 total score), and higher mean fasting blood glucose. In contrast, women had higher mean BMI, WC, HDL-C compared to men, at both waves. Among incident outcomes, central obesity was markedly higher among women compared to men, with no difference noted for incident obesity or incident MetS. Nevertheless, in the cross-sectional data, obesity and central obesity were both significantly more prevalent among women compared to men at both waves, while MetS prevalence was higher among women only at follow-up.

Table 3 shows associations of *VDR* and *MEGALIN* haplotypes with incident metabolic disturbances (obesity, MetS, and individual MetS components), stratifying by sex. Among all key results, only survived correction for multiple testing. In fact, among men, incident hypertension was inversely related to the $MEGALIN_1$ haplotype (HR = 0.45, 95% CI:0.23–0.90, p = 0.024). Though not surviving correction for multiple testing, this haplotype was also inversely related to incident MetS among men. Similarly, incident hyperglycemia was linked to VDR_1 haplotype in men. Among women, VDR_3 was inversely related to incident central obesity, and VDR_2 was directly associated with incident hypertension. $MEGALIN_2$ was consistently inversely related to incident hypertension and incident hyperglycemia among women. The latter association differed significantly between sexes.

Cross-sectional associations between the selected *VDR* and *MEGALIN* haplotypes and the main metabolic disturbances are presented in Tables 4 (baseline outcomes) and 5 (follow-up outcomes). There was a linear dose-response direct association between VDR_2 and prevalent obesity and MetS at baseline, with no significant sex differences, (OR = 1.60, 95% CI:1.11–2.31, p = 0.012). Moreover, VDR_3 was inversely related to prevalent MetS at baseline among men, (OR = 0.40, 95% CI:0.19–0.81, p = 0.011), an association that differed significantly by sex ($P < 0.05$ for sex × SNPHAP interaction term). Both of these findings survived correction for multiple testing. The associations of *VDR* and *MEGALIN* SNPHAPs with follow-up outcomes did not survive correction for multiple testing. Among those, VDR_2 was positively associated with prevalent obesity, overall and among women, a finding consistent with the baseline outcome. *MEGALIN* haplotypes were not associated with prevalent baseline or follow-up outcomes of obesity, central obesity and MetS. A sensitivity analysis that included only basic socio-demographic factors yielded similar results.

Table S2 presents supplemental results for single SNP analyses for *VDR* and *MEGALIN* in relation to MetS outcomes, stratifying by gender. For incident MetS, overall, 15 SNP passed correction for multiple testing, of which one had a p = 0.001 (*MEGALIN* SNP: rs148386284: T allele, HR = 2.63, 95% CI:1.45–4.76). While many other SNPs were also associated with incident MetS, the ones that had $p \leq 0.01$ were among women, including *MEGALIN* SNP rs830966: G allele, HR = 4.28, 95% CI:1.80–10.20) and 6 protective *VDR* SNPs located near a well-studied SNP names Cdx-I, rs11568250, whose C allele was also inversely related to incident MetS among women (HR = 0.11, 95%CI: 0.02–0.47, p = 0.003). Similarly, both *VDR* and *MEGALIN* single SNPs had significant associations with baseline and follow-up MetS outcomes, overall and among men and women, with few SNPs overlapping or being highly correlated with those that affected the incident outcome (e.g. incident MetS vs. follow-up MetS in women: rs830966-rs830969, rs2107301). Moreover, among the selected SNPs for VDR haplotypes, rs731236 (TaqI G > A) was associated with a reduced odds of baseline MetS (OR = 0.69, 95% CI: 0.50, 0.96, p = 0.029). Similarly, rs1544410 (BsmI G > A) was linked to an increased odds of baseline MetS among men (OR = 1.73, 95% CI: 1.01, 3.00, p = 0.045).

Discussion

This study examined associations of selected haplotypes from SNPs in four *VDR* [rs1544410(BsmI:G/A); rs7975232(ApaI:A/C); rs731236(TaqI:G/A)], and two *MEGALIN* [rs3755166:G/A; rs2075252:C/T; rs2228171:C/T] gene haplotypes with longitudinal (n = 294–466) and cross-sectional (n = 539) metabolic outcomes among African Americans over a mean period of ~5 y of follow-up. Among key findings, in men, incident hypertension and MetS were inversely related to $MEGALIN_1$ (GCC), and in women, $MEGALIN_2$ (ACC) was consistently inversely related to incident hypertension and incident hyperglycemia. Among men, incident hyperglycemia was positively associated with VDR_1 (GCA:baT), and among women, VDR_2 (AAG:BAt) was directly associated with incident hypertension and VDR_3 (GAA:Bat) was inversely related to incident central obesity. Overall, there was a direct, linear dose-response association between VDR_2 (AAG:BAt), obesity and MetS at baseline. Moreover, VDR_3 (GAA:bAT) was inversely related to baseline MetS among men, which differed significantly by sex. No associations were detected between *MEGALIN* haplotypes and outcomes at baseline or follow-up and 3 associations survived correction for multiple testing [VDR_2 vs. baseline MetS (overall), VDR_3 vs. baseline MetS (men) and $MEGALIN_1$ vs. incident hypertension in men].

Recent studies with cross-sectional or case-control design have examined *VDR* polymorphisms as risk markers for central adiposity and related metabolic disorders[6,14–23]. However, none of these studies included African-American adults in their samples. When examining *VDR* SNP relationships with adiposity, a recent cross-sectional study (176 randomly selected men aged 25–65 y) found that homozygous *BsmI* (BB: AA *vs.* GG) was associated with higher BMI (29.0 *vs.* 26.8 kg/m^2, p = 0.024) and higher WC (101.8 vs. 96.2 cm, p = 0.014)[15]. A similar finding was observed in another cross-sectional study of 153 women among whom body weight and fat mass were positively associated with the "BB" genotype of VDR SNP BsmI[16]. Similarly, in a third cross-sectional study, an association was found between a homozygous rare variant of rs3782905 located in the 3' *VDR* region (LD of rs3782905 with BsmI in White Hapmap is ~0.42) and 4.4 cm larger mean WC when compared with the homozygous common variant (Bonferroni-adjusted p = 0.004)[6]. These consistent findings for BsmI "A" allele

	Prevalent metabolic disturbance								
	All (N = 539)			Men (N = 230)			Women (N = 309)		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Obesity: Models A-F									
VDR_1: GCA (0,1,2)	0.88	(0.67;1.15)	0.36	1.18	(0.75;1.86)	0.46	0.76	(0.53;1.10)	0.14
VDR_2: AAG (0,1,2)	**1.44**	**(1.02;2.03)**	**0.038**	1.22	(0.70;2.14)	0.49	***1.50***	***(0.94;2.40)***	***0.089***
VDR_3: GAA (0,1,2)	0.95	(0.67;1.35)	0.78	0.74	(0.40;1.36)	0.34	1.04	(0.66;1.65)	0.84
VDR_4: AAA(0,1,2)	1.21	(0.75;1.95)	0.44	1.21	(0.56;2.63)	0.63	1.30	(0.67;2.50)	0.43
$MEGALIN_1$: GCC (0,1,2)	1.11	(0.80;1.56)	0.53	0.86	(0.48;1.53)	0.61	1.16	(0.74;1.82)	0.51
$MEGALIN_2$: ACC (0,1,2)	0.95	(0.70;1.32)	0.78	1.00	(0.58;1.73)	1.00	1.03	(0.67;1.60)	0.90
Central obesity: Models A-F									
VDR_1: GCA (0,1,2)	0.88	(0.70;1.16)	0.35	1.31[3]	(0.85;2.03)	0.22	**0.66**	**(0.44;0.98)**	**0.040**
VDR_2: AAG (0,1,2)	1.36	(0.93;1.99)	0.12	1.21	(0.71;2.05)	0.50	***1.76***	***(0.92;3.36)***	***0.083***
VDR_3: GAA (0,1,2)	1.14	(0.78;1.70)	0.50	0.80	(0.42;1.36)	0.36	1.37	(0.79;2.36)	0.26
VDR_4: AAA(0,1,2)	0.88	(0.53;1.48)	0.64	1.06	(0.48;2.34)	0.88	0.80	(0.38;1.69)	0.56
$MEGALIN_1$: GCC (0,1,2)	1.31	(0.91;1.88)	0.14	1.16	(0.68;2.02)	1.00	1.30	(0.78;2.17)	0.32
$MEGALIN_2$: ACC (0,1,2)	0.93	(0.66;1.32)	0.69	0.91	(0.53;1.55)	0.73	1.04	(0.63;1.74)	0.87
Metabolic syndrome: Models A-F									
VDR_1: GCA (0,1,2)	0.81	(0.59;1.10)	0.18	0.99	(0.60;1.64)	0.96	0.69	(0.44;1.08)	0.10
VDR_2: AAG (0,1,2)	**1.60**	**(1.11;2.31)**	**0.012**	**1.91**	**(1.05;3.48)**	**0.034**	***1.62***	***(0.97;2.70)***	***0.063***
VDR_3: GAA (0,1,2)	0.89	(0.60;1.31)	0.54	**0.40**[3]	**(0.19;0.81)**	**0.011**	1.23	(0.74;2.07)	0.43
VDR_4: AAA(0,1,2)	0.85	(0.50;1.48)	0.57	1.09	(0.46;1.99)	0.84	0.70	(0.32;1.56)	0.39
$MEGALIN_1$: GCC (0,1,2)	0.76	(0.52;1.13)	0.16	0.88	(0.45;1.74)	0.72	***0.64***	***(0.38;1.07)***	***0.091***
$MEGALIN_2$: ACC (0,1,2)	1.13	(0.79;1.63)	0.50	1.17	(0.62;2.19)	0.64	1.21	(0.74;1.98)	0.45

Table 4. VDR and MEGALIN SNP haplotype (SNPHAP) associations with prevalent metabolic disturbances (V1): multiple logistic regression models, ($n = 539$); HANDLS study. *Abbreviations*: BMI = body mass index (calculated as weight in kg/square of height in meters); SNP = Single Nucleotide polymorphism; SNPHAP = SNP haplotype; V1 = Visit 1; *VDR* = Vitamin D receptor gene; Note that VDR_1, VDR_2, VDR_3 denote *VDR* SNPHAP, whereas $MEGALIN_1$, $MEGALIN_2$ and $MEGALIN_3$ denote *MEGALIN* SNPHAP. *Note*: Shaded estimated indicate significance upon correction for multiple testing. Models A-F indicate that each haplotype was entered in a separate regression model to estimate its association with different metabolic outcomes. [1]See Table 1 for more details on definition the SNP haplotypes. (0,1,2) refers to ordinal coding with "0", "1" and "2" copies of each haplotype. Three *VDR* SNP were combined to form the haplotypes, namely BsmI, ApaI and TaqI. Only haplotypes 1 and 2 were selected for *MEGALIN* since their overall prevalence was >10%. [2]Models were adjusted for age, sex, poverty status, education, current smoking status, current illicit drug use, self-rated health, total energy intake, HEI-2010 total score, 10 principal components for population structure, and the inverse mills ratio. [3]$P < 0.05$ for null hypothesis that sex × SNPHAP interaction term = 0 in a model where main effect of sex was added.

dosage increasing the risk for obesity, were replicated with other related phenotypes, including T2D, fasting glucose level, LDL-Cholesterol and coronary heart disease risk in recent studies[17–20]. Using data from Baltimore Longitudinal Study of Aging, a previous study found that only the *Apa*I SNP ("C" allele dosage) significantly increased the odds of higher waist-to-hip ratio over time (P-trend = 0.024)[14]. These findings are consistent with ours, given that the "B" allele of BsmI corresponds to the "A" risk allele. In fact, findings from our present study indicated a positive association between MetS and the BAt *VDR* haplotype (i.e. VDR_2) in the overall population and an inverse relationship with the bAT (i.e. VDR_3) haplotype among men. Many other key results not surviving correction for multiple testing were generally trending in that same direction for various metabolic outcomes. Moreover, *MEGALIN* polymorphisms influenced central adiposity in Whites residing in Baltimore city: rs2075252 "TT" was associated with elevated waist to hip ratio at one point in time compared with rs2075252 "CC"[14]. Our finding with *MEGALIN*1 (GCC for rs3755166:G/A; rs2075252:C/T and rs2228171:C/T) being inversely related to incident hypertension indicates that in fact, a "C" allele for the middle SNP (rs2075252:C/T) may be protective against various obesity-related metabolic disturbance, particularly hypertension incidence rate. However, more studies are needed in diverse samples to replicate this finding.

Few previous studies have examined *VDR* SNPHAP as predictors of metabolic and cardiovascular outcomes. Despite earlier null findings, (e.g[21].) more recent studies indicated that in fact BAt (VDR_2) was associated with increased obesity risk, while the haplotype "GAG", which was rare among our African-American urban adult population, was associated with a reduced risk of obesity[22]. Moreover, in a population-based study of men and women aged 55–80 y, each baT haplotype copy was associated with a 20% increased likelihood of ECG-confirmed myocardial infarction, adjusting for key confounders[23]. Similarly, in the BLSA study, an increased risk of longitudinal increase in WC among White women was uncovered with each baT haplotype copy[14]. In our present study, incident hyperglycemia risk was positively associated with baT, particularly among African-American men. Nevertheless, BAt, a less common haplotype in this population, was associated with a greater risk of incident hypertension in African-American women and with a greater likelihood of prevalent obesity and baseline MetS

	Prevalent metabolic disturbance								
	All (N = 539)			Men (N = 230)			Women (N = 309)		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Obesity: Models A-F									
VDR_1: GCA (0,1,2)	0.89	(0.68;1.16)	0.37	1.05	(0.68;1.60)	0.83	0.78	(0.55;1.11)	0.17
VDR_2: AAG (0,1,2)	**1.43**	**(1.01;2.02)**	**0.044**	1.08	(0.63;1.84)	0.78	**1.79**	**(1.09;2.95)**	**0.023**
VDR_3: GAA (0,1,2)	0.96	(0.69;1.36)	0.85	0.94	(0.53;1.66)	0.82	0.99	(0.63;1.56)	0.96
VDR_4: AAA(0,1,2)	1.17	(0.72;1.88)	0.53	1.32	(0.62;2.81)	0.47	1.19	(0.61;2.29)	0.61
$MEGALIN_1$: GCC (0,1,2)	1.08	(0.77;1.50)	0.67	0.95	(0.54;1.67)	0.85	1.13	(0.73;1.77)	0.56
$MEGALIN_2$: ACC (0,1,2)	1.06	(0.76;1.46)	0.74	1.17	(0.68;1.99)	0.57	1.05	(0.68;1.62)	0.82
Central obesity: Models A-F									
VDR_1: GCA (0,1,2)	1.03	(0.76;1.40)	0.83	1.10	(0.72;1.69)	0.65	1.07	(0.66;1.73)	0.79
VDR_2: AAG (0,1,2)	1.18	(0.79;1.77)	0.41	0.90	(0.54;1.52)	0.71	1.75	(0.82;3.77)	0.15
VDR_3: GAA (0,1,2)	1.02	(0.69;1.52)	0.92	1.22	(0.69;2.14)	0.49	0.84	(0.46;1.56)	0.59
VDR_4: AAA(0,1,2)	1.30	(0.73;2.32)	0.37	1.55	(0.71;3.38)	0.27	0.99	(0.41;2.41)	0.98
$MEGALIN_1$: GCC (0,1,2)	1.04	(0.71;1.53)	0.84	0.77	(0.44;1.35)	0.36	1.35	(0.72;2.52)	0.35
$MEGALIN_2$: ACC (0,1,2)	1.10	(0.76;1.62)	0.61	1.26	(0.74;2.15)	0.40	1.05	(0.57;1.94)	0.87
Metabolic syndrome: Models A-F									
VDR_1: GCA (0,1,2)	0.96	(0.71;1.31)	0.81	1.46[3]	(0.88;2.44)	0.14	***0.68***	***(0.43;1.06)***	***0.086***
VDR_2: AAG (0,1,2)	1.25	(0.86;1.83)	0.25	0.87	(0.42;1.80)	0.71	***1.60***	***(0.97;2.63)***	***0.063***
VDR_3: GAA (0,1,2)	1.13	(0.75;1.68)	0.56	0.69[3]	(0.32;1.50)	0.35	1.49	(0.89;2.49)	0.13
VDR_4: AAA(0,1,2)	0.60	(0.31;1.14)	0.12	0.72	(0.26;1.95)	0.51	0.52	(0.21;1.28)	0.16
$MEGALIN_1$: GCC (0,1,2)	0.75	(0.50;1.11)	0.15	0.70	(0.34;1.44)	0.33	0.72	(0.43;1.21)	0.22
$MEGALIN_2$: ACC (0,1,2)	1.08	(0.74;1.58)	0.68	1.07	(0.55;2.12)	0.83	1.17	(0.71;1.92)	0.54

Table 5. VDR and MEGALIN SNP haplotype (SNPHAP) associations with prevalent metabolic disturbances (V2): multiple logistic regression models, ($n = 539$); HANDLS study. *Abbreviations*: BMI = body mass index (calculated as weight in kg/square of height in meters); SNP = Single Nucleotide polymorphism; SNPHAP = SNP haplotype; V2 = Visit 2; *VDR* = Vitamin D receptor gene; Note that VDR_1, VDR_2, VDR_3 denote *VDR* SNPHAP, whereas $MEGALIN_1$, $MEGALIN_2$ and $MEGALIN_3$ denote *MEGALIN* SNPHAP. [1]See Table 1 for more details on definition the SNP haplotypes. (0,1,2) refers to ordinal coding with "0", "1" and "2" copies of each haplotype. Three *VDR* SNP were combined to form the haplotypes, namely BsmI, ApaI and TaqI. Only haplotypes 1 and 2 were selected for *MEGALIN* since their overall prevalence was > 10%. [2]Models were adjusted for age, sex, poverty status, education, current smoking status, current illicit drug use, self-rated health, total energy intake, HEI-2010 total score, 10 principal components for population structure, and the inverse mills ratio. [3]$P < 0.05$ for null hypothesis that sex × SNPHAP interaction term = 0 in a model where main effect of sex was added.

in the total African-American urban population. The latter finding (i.e. VDR_2 vs. baseline MetS) was the only one that survived correction for multiple testing in the total population.

In terms of biological mechanisms, a greater *VDR* expression in adipocytes decreases energy expenditure markedly leading to increased adiposity. Further, VDR agonists reduce pro-inflammatory cytokines and D3 reduces high-glucose and LPS-induced TNFα and TGFβ release, suggesting a protective mechanism[22]. Moreover, high BMI is associated with low circulating 25(OH)D due to sequestration in adipose tissue[43]. Importantly, longer *VDR* BsmI polyA repeats exhibited less stability and translated less efficiently into VDR protein, resulting in a decreased vitamin D response, muscle cell inhibition and adipocyte differentiation[16]. In addition to the association of calcium and high Vitamin D intakes, vitamin D may also reduce hepatic synthesis of triglycerides and upregulate adiponectin expression, which in turn could reduce obesity and related metabolic disorders[44]. In the African-American population, *VDR* can trigger adiposity by modulating *VDR*-dependent molecular components of adipogenesis such as PPAR-γ and EBPα and thus inhibiting corresponding adipocyte differentiation[45]. Further, *VDR* variants may directly influence the binding of vitamin D and mediate various downstream effects on genes known to be VDR-responsive, thus influencing associated phenotypes[6]. Particularly for T2D, VDR may act as a transcription factor for β cell insulin secretion regulation, thereby affecting lipid metabolism[46].

Our study has several strengths, which include its longitudinal follow-up design, a large sample of a diverse urban population, and the extensive use of advanced statistical methods, through the combination of survival analysis, logistic regression, haplotype analysis and adjustment for selection biases.

Nevertheless, our study has notable limitations. First, our final analytic sample was likely selected in a non-random manner, whereby certain groups were over-sampled when compared with the original African-American sample in HANDLS. A 2-stage Heckman selection model was used to diminish those incurred biases[38]. Second, first-vist age and between-visit duration varied across participants, which may incur some imbalance in the data structure. Survival analysis methods were used to adjust for this imbalance. Moreover, our study had limited power to examine gene-environment interaction, particularly with 25(OH)D in serum or dietary intakes of

vitamin D. Finally, positive results may have been chance findings, while negative findings may have been caused by lack of adequate power.

In conclusion, *VDR* and *MEGALIN* gene variations can affect the prevalence of MetS and the incidence of hypertension in a sex-specific manner, respectively, among African-American urban adults. Those study findings provide novel insights into the genetic variants at those gene loci and their association with susceptibility to cardiometabolic risk, including the metabolic syndrome among populations of African descent. Further functional studies of *VDR* and *MEGALIN* gene in relation to cardiometabolic risk can provide important validation for our results and can contribute to our understanding of how vitamin D metabolism-related genes can influence metabolic disorders in various populations. In addition, our findings if replicated by others can establish the need for a genetic screening test for *VDR* and *MEGALIN* polymorphisms. Thus, further large epidemiologic studies of similar populations are required to replicate our current findings.

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Author Contributions

M.A.B.: Conceptualization, plan of analysis, data management, statistical analysis, literature review, write-up of the manuscript. S.H.: Literature search and review, assistance with statistical analysis, write-up of parts of the manuscript, revision of manuscript. S.A.T.: Data management, write-up of parts of the manuscript, revision of the manuscript. J.A.C.: Literature review, write-up of parts of the manuscript, revision of the manuscript. M.K.: Data acquisition, write-up of parts of the manuscript, revision of the manuscript. H.A.B.: Plan of analysis, literature review, write-up of parts of the manuscript, revision of the manuscript. M.K.E.: Data acquisition, write-up of parts of the manuscript, revision of the manuscript. A.B.Z.: Data acquisition, plan of analysis, write-up of parts of the manuscript, revision of manuscript. All authors read and approved the final version of the paper.

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VITAMIN D METABOLISM-RELATED GENE HAPLOTYPES AND THEIR ASSOCIATION WITH METABOLIC DISTURBANCES AMONG AFRICAN-AMERICAN URBAN ADULTS

May A. Beydoun[1,*]; Sharmin Hossain[1]; Salman M. Tajuddin[1]; Jose A. Canas[2]; Marie Kuczmarski[3]; Hind A. Beydoun[4]; Michele K. Evans[1§]; Alan B. Zonderman[1§]

[1] Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIA/NIH/IRP, Baltimore, MD.

[2] Pediatric Endocrinology, Nemours Children's Clinic, Jacksonville, FL.

[3]Department of Behavioral Health and Nutrition, University of Delaware, Newark, DE.

[4] Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD.

Supplemental Methods 1: Genetic data quality control

Sample quality control inclusion criteria were: **(1)** concordance between self-reported sex and X-chromosome estimated sex; **(2)** sample call rate >95%, **(3)** concordance between self-reported African ancestry and ancestry estimated using genotyped SNPs, and **(4)** proportional sharing of genotypes < 15% between samples, excluding close relatives from the final sample. SNPs in HANDLS were selected when the following criteria were met: **(1)** Hardy-Weinberg equilibrium p-value (HWE $P > 10^{-7}$); **(2)** Missing by haplotype $P > 10^{-7}$; **(3)** Minor allele frequency>0.01, and **(4)** SNP call rate >95%. Quality control and data management for each genotype was conducted using PLINKv1.06.[1] Cryptic relatedness was estimated via pairwise identity by descent analyses in PLINK and confirmed using RELPAIR.[2] STRUCTUREv2.3 [3-5] and multidimensional scaling (MDS) function in PLINKv1.06 were applied to determine ancestry among HANDLS participants. HANDLS participants with component vector estimates consistent with the HapMap African ancestry samples for the first 4 component vectors were included. Moreover, in a sensitivity analysis, we adjusted for all the first 10 principal components obtained from genotype data with MDS to control for residual effects of population structure.[6]. SNPs that passed quality control criteria were used for genotype imputation with MACH and minimac software (http://www.sph.umich.edu/csg/abecasis/mach/). The 1000 Genomes Project phase 1 alpha freeze multiethnic panel were used as a reference population for genotype imputation. SNPs with imputation quality measure of $R^2<0.3$ or minor allele frequency of <1% were excluded from further analyses.

Gene	SNP	Allele1	Allele2	Minor allele frequency (MAF)	Genotyped or imputed	Genotype call rate	R-square
VDR	rs731236	A	G	0.28034	Genotyped	0.996	-
VDR	rs7975232	C	A	0.37811	Genotyped	0.999	-
VDR	rs1544410	C	T	0.29485	Genotyped	0.999	-
MEGALIN	rs2075252	C	T	0.10177	Genotyped	0.998	-
MEGALIN	rs2228171	C	T	0.20141	Imputed	-	0.991
MEGALIN	rs3755166	G	A	0.3019	Genotyped	0.999	-

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Supplemental Methods 2: Single SNP analysis for all available high quality polymorphisms on the VDR and MEGALIN genes region.

758 SNPs in and around VDR and MEGALIN genes were found in the HANDLS database, that were of good quality based on the same criteria described in supplemental method 1. A secondary analysis was conducted whereby each SNP was entered into the same models as for SNPHAPs along with the same set of covariates and the same series of incident and prevalent metabolic syndrome outcomes, stratifying by sex. Effect modification by sex was also tested. The critical p-value was set at 0.01 for overall analysis and 0.02 for sex-specific analyses. Only statistically significant findings after correction for multiple testing are presented. Noteworthy results with $p \leq 0.001$ are highlighted. Below is the complete list of SNPs included in the analyses, along with the allele dosage definition based on Al1, and Mean Allele Frequency of Al1. CHR = 2 for *MEGALIN* and CHR=12 for *VDR*.

TABLE S1. Selected SNPs for supplemental analysis

CHR	SNP	Al1	Al2	MAF
2	rs7566044	A	G	0.2529
2	rs72888673	A	G	0.07764
2	rs79004576	A	G	0.0498
2	rs12328794	T	C	0.2373
2	rs12105342	T	C	0.2012
2	rs3815574	A	C	0.2168
2	rs2302698	A	G	0.2026
2	rs736020	T	C	0.2026
2	rs10192264	T	C	0.2993

2	rs4668119	G	A	0.3052
2	rs6750251	G	C	0.4097
2	rs12474309	C	G	0.1299
2	rs75950705	A	T	0.07959
2	rs62172561	C	T	0.03564
2	rs4668120	C	G	0.4834
2	rs75825993	C	G	0.1274
2	rs7606912	G	A	0.4023
2	rs79890698	T	G	0.1416
2	rs4667590	G	C	0.3423
2	rs75180829	C	T	0.1436
2	rs1861609	G	A	0.2476
2	rs2389598	T	C	0.4932
2	rs113349208	G	A	0.1431
2	rs6433105	T	C	0.2334
2	rs2111187	C	T	0.4907
2	rs4668121	T	G	0.4331
2	rs73028985	A	G	0.1084
2	rs1990702	T	C	0.1821
2	rs7574148	C	T	0.01904
2	rs73028988	T	C	0.1084
2	rs73028989	C	A	0.1089
2	rs10191750	A	G	0.4102
2	rs6433106	T	C	0.2808
2	rs6433107	T	G	0.1821
2	rs78597444	A	G	0.01123
2	rs78655335	T	A	0.1089
2	rs12466193	T	G	0.1836

2	rs12478045	C	G	0.3198
2	rs13406401	A	G	0.3711
2	rs55670659	T	C	0.4028
2	rs11884346	C	T	0.3408
2	rs73028996	G	A	0.1108
2	rs7598209	T	C	0.1685
2	rs1003456	A	T	0.1704
2	rs73030803	G	T	0.1094
2	rs6754932	C	T	0.1895
2	rs11691854	T	C	0.3911
2	rs139023066	G	C	0.3823
2	rs150914001	A	C	0.2964
2	rs144260784	G	A	0.1069
2	rs115648286	C	T	0.3447
2	rs58389457	G	A	0.333
2	rs7576280	G	A	0.1792
2	rs11693676	G	C	0.1138
2	rs139334150	C	T	0.2314
2	rs11892075	A	G	0.3906
2	rs140706266	T	C	0.1084
2	rs4264540	T	G	0.2344
2	rs11674531	G	T	0.4512
2	rs6746604	C	G	0.314
2	rs990627	T	C	0.312
2	rs990626	A	G	0.312
2	rs73970130	C	A	0.1826
2	rs2268380	A	G	0.3125
2	rs2268379	G	A	0.4561

2	rs2268378	A	G	0.4346
2	rs6725805	G	A	0.4385
2	rs16856488	G	A	0.2114
2	rs2075253	G	A	0.249
2	rs6733111	G	A	0.293
2	rs6733122	A	G	0.3672
2	rs146901930	A	G	0.08398
2	rs2284681	C	A	0.3672
2	rs68155726	T	G	0.3345
2	rs2284680	C	A	0.3711
2	rs4668122	A	G	0.4014
2	rs2239592	C	T	0.29
2	rs2239591	T	C	0.3701
2	rs2239590	A	T	0.3701
2	rs2239589	G	T	0.3706
2	rs4667591	G	T	0.2246
2	rs41268687	A	G	0.209
2	rs4667592	G	A	0.4736
2	rs55681838	C	T	0.05029
2	rs6761244	A	G	0.4517
2	rs1123904	A	C	0.4087
2	rs1123905	T	C	0.4087
2	rs12692892	G	A	0.4497
2	rs10192078	T	C	0.4541
2	rs741376	A	C	0.4087
2	rs72874715	T	A	0.06104
2	rs755631	C	A	0.4844
2	rs17848195	A	G	0.1865

2	rs3944004	C	A	0.2832
2	rs4667593	A	G	0.4102
2	rs4667594	T	A	0.4014
2	rs11679947	G	A	0.4097
2	rs10490132	C	A	0.4097
2	**rs2075252**	**T**	**C**	**0.1021**
2	rs2075251	T	A	0.1387
2	rs3815573	A	G	0.377
2	rs13021137	G	T	0.4941
2	rs6759013	A	G	0.3882
2	rs6730825	C	T	0.4863
2	rs13011165	T	C	0.3882
2	rs13034796	G	A	0.376
2	rs2268377	C	A	0.4624
2	rs2268376	T	C	0.3882
2	rs9646777	G	A	0.4932
2	rs9646778	T	C	0.3882
2	rs3821124	T	G	0.4624
2	rs2268375	G	A	0.4546
2	rs2268374	G	T	0.1021
2	rs11884342	A	G	0.4595
2	rs11896574	T	A	0.4272
2	rs2229268	G	A	0.05176
2	rs2239602	C	T	0.05078
2	rs2239601	A	G	0.2515
2	rs4140872	C	T	0.1011
2	rs7559094	A	T	0.25
2	rs67931300	C	T	0.1875

2	rs4497843	A	G	0.2212
2	rs17848190	C	T	0.1201
2	rs17848189	A	C	0.09033
2	rs2075250	C	T	0.09033
2	rs2024481	A	C	0.4092
2	rs2229265	T	C	0.3423
2	rs2193196	T	C	0.1938
2	rs7565788	T	C	0.2388
2	rs741378	G	A	0.4263
2	rs10191692	C	T	0.4053
2	rs7421492	C	T	0.4009
2	rs112597789	A	G	0.08398
2	rs2892803	C	T	0.4033
2	rs9789747	C	T	0.08838
2	rs9287910	C	T	0.3076
2	rs9287911	A	T	0.2368
2	rs6744473	T	A	0.3491
2	rs17848180	T	C	0.04297
2	rs3213759	T	G	0.2158
2	rs10169879	T	C	0.2437
2	rs10204688	C	T	0.1885
2	rs7588584	T	C	0.2412
2	rs2024480	A	G	0.1885
2	rs2284679	C	T	0.2495
2	rs6744155	G	A	0.2412
2	rs2284678	A	G	0.2324
2	rs2284677	G	A	0.2412
2	rs2284676	G	A	0.3203

2	rs4287730	G	C	0.2188
2	rs6747214	C	T	0.2524
2	rs59363833	C	T	0.2793
2	rs16856558	A	G	0.2397
2	rs10210408	T	C	0.4229
2	rs1548936	C	T	0.2002
2	rs1972589	C	T	0.2612
2	rs57926641	C	T	0.2783
2	rs7565822	G	A	0.4819
2	rs7592152	A	C	0.08936
2	rs16856573	T	C	0.2031
2	rs4331469	A	C	0.4736
2	rs2389589	A	G	0.2695
2	rs3770604	T	A	0.2715
2	rs13388593	T	C	0.2349
2	rs3821125	T	C	0.4834
2	rs2075248	T	C	0.1919
2	rs73971311	T	G	0.1875
2	rs11886626	T	C	0.2036
2	rs2075247	T	C	0.3867
2	rs10490131	G	A	0.03174
2	rs58687448	C	T	0.2007
2	rs77463292	T	C	0.03174
2	rs7557964	C	T	0.2949
2	rs1972588	T	G	0.008789
2	rs7578722	C	T	0.1963
2	**rs2228171**	**T**	**C**	**0.2007**
2	rs2302696	T	C	0.4297

2	rs73033887	T	C	0.2764
2	rs10169232	C	G	0.2842
2	rs16856592	C	A	0.2803
2	rs16856593	A	G	0.271
2	rs16856596	A	G	0.1992
2	rs62172607	A	G	0.3027
2	rs62172609	A	G	0.3022
2	rs16823023	C	T	0.1992
2	rs11898106	G	A	0.2764
2	rs73033899	T	C	0.27
2	rs73971315	G	T	0.2993
2	rs28454851	A	G	0.3779
2	rs77726104	C	T	0.1313
2	rs11687903	G	T	0.4277
2	rs13401581	A	G	0.3779
2	rs79399342	G	T	0.1318
2	rs16856600	A	G	0.2031
2	rs2239600	T	C	0.4268
2	rs2284675	A	G	0.4268
2	rs2239599	C	T	0.4302
2	rs6725137	T	C	0.3003
2	rs13410285	A	T	0.249
2	rs13397109	C	G	0.2993
2	rs35114151	G	A	0.1055
2	rs13417389	C	T	0.3052
2	rs2268373	G	C	0.3535
2	rs2268372	A	T	0.3276
2	rs10200740	C	T	0.3633

2	rs10200859	C	T	0.3535
2	rs10188487	T	C	0.3276
2	rs79503405	T	G	0.2705
2	rs62172612	C	G	0.09521
2	rs75569504	G	A	0.3496
2	rs116247504	C	T	0.2417
2	rs112172369	C	G	0.2847
2	rs10170902	G	A	0.1704
2	rs4668124	A	C	0.07031
2	rs77711606	C	T	0.2085
2	rs4001547	G	C	0.06982
2	rs11689553	G	C	0.05273
2	rs10201691	A	G	0.2734
2	rs13422498	T	G	0.1709
2	rs10201911	T	C	0.2012
2	rs6718884	C	T	0.4941
2	rs11886219	C	T	0.4175
2	rs2302695	G	C	0.2764
2	rs75092581	A	G	0.1675
2	rs17848164	T	C	0.2959
2	rs2052298	A	T	0.3525
2	rs2052297	C	T	0.3521
2	rs10190812	T	C	0.2388
2	rs2052296	C	A	0.2368
2	rs62172631	A	G	0.3965
2	rs11897009	T	C	0.2383
2	rs11886185	T	A	0.2505
2	rs11886318	A	C	0.2754

2	rs13417486	T	C	0.2339
2	rs13431061	C	T	0.2842
2	rs62172632	T	G	0.2163
2	rs7600336	C	T	0.314
2	rs2300447	C	A	0.3716
2	rs2300446	T	C	0.3672
2	rs2193195	T	C	0.4736
2	rs2193194	G	A	0.3452
2	rs2193193	G	A	0.2749
2	rs2216239	C	T	0.3423
2	rs3815572	T	C	0.27
2	rs2268370	A	C	0.3115
2	rs9283479	C	T	0.3149
2	rs9646731	A	G	0.2646
2	rs7569236	T	C	0.2339
2	rs4606889	T	C	0.3149
2	rs4302191	C	G	0.2808
2	rs6719440	C	T	0.3149
2	rs6747692	T	A	0.3291
2	rs2268369	A	C	0.2822
2	rs2268368	T	C	0.3335
2	rs2268367	A	C	0.2822
2	rs2268366	A	T	0.3335
2	rs13389381	C	T	0.376
2	rs11902433	C	T	0.29
2	rs34951037	A	T	0.3208
2	rs2075246	A	G	0.2886
2	rs982810	A	G	0.2871

2	rs13383183	A	C	0.3799
2	rs35836996	T	A	0.3779
2	rs6433109	A	C	0.2764
2	rs3915725	A	G	0.2383
2	rs4668127	A	G	0.3643
2	rs4668128	G	A	0.2817
2	rs2302694	A	G	0.3848
2	rs2302693	T	C	0.2729
2	rs2302692	C	T	0.3574
2	rs3926693	T	C	0.3574
2	rs1816039	T	C	0.2388
2	rs4667597	A	G	0.2056
2	rs3821126	A	G	0.3164
2	rs1362996	G	A	0.4009
2	rs3821127	A	G	0.2817
2	rs3821128	T	C	0.2739
2	rs2239598	G	A	0.4453
2	rs2239597	C	A	0.3496
2	rs2239596	C	T	0.3877
2	rs2239595	A	G	0.03174
2	rs2239594	C	T	0.2778
2	rs6713797	A	T	0.3242
2	rs151020693	C	T	0.1318
2	rs6752778	A	C	0.3223
2	rs6724600	G	T	0.4556
2	rs13401167	G	A	0.1772
2	rs114534086	C	T	0.1338
2	rs4668129	G	A	0.3804

2	rs115452726	A	C	0.1357
2	rs148175287	A	G	0.1323
2	rs114658487	T	C	0.1323
2	rs2229267	A	G	0.3623
2	rs78967293	T	G	0.1323
2	rs78008770	A	T	0.1323
2	rs12987817	G	A	0.106
2	rs2268365	C	T	0.03174
2	rs78265059	T	C	0.1323
2	rs830973	A	G	0.3823
2	rs34915742	G	C	0.1323
2	rs76714416	G	A	0.1323
2	rs76838238	T	C	0.1323
2	rs2239593	A	G	0.08154
2	rs111495150	C	T	0.1323
2	rs12615180	A	C	0.008301
2	rs78828988	T	C	0.1318
2	rs77416334	G	T	0.1318
2	rs3755164	A	C	0.003418
2	rs10490130	C	A	0.1729
2	rs831040	C	T	0.4004
2	rs831041	T	G	0.312
2	rs831042	T	C	0.4019
2	rs2075254	G	A	0.312
2	rs56377101	A	G	0.2075
2	rs12613980	T	G	0.1504
2	rs831043	T	C	0.312
2	rs2075249	T	G	0.272

2	rs831044	A	T	0.3906
2	rs16823029	A	C	0.1836
2	rs831046	G	A	0.07764
2	rs830956	C	T	0.3438
2	rs830957	C	T	0.4297
2	rs830959	C	T	0.3438
2	rs830960	C	T	0.3438
2	rs1421509	T	C	0.3135
2	rs2241190	T	C	0.3203
2	rs33954745	G	A	0.144
2	rs35583956	T	A	0.1992
2	rs830982	G	A	0.3872
2	rs13025890	G	C	0.145
2	rs830983	A	G	0.395
2	rs12988804	T	C	0.1855
2	rs1096456	T	C	0.3174
2	rs138822865	A	C	0.06885
2	rs36198025	G	A	0.1724
2	rs141755776	T	C	0.006836
2	rs830989	A	G	0.3794
2	rs830991	T	C	0.3716
2	rs35994058	T	A	0.1714
2	rs68108873	C	T	0.1343
2	rs35853478	T	C	0.1372
2	rs2673175	T	G	0.165
2	rs4667599	G	A	0.4316
2	rs4613240	C	T	0.06885
2	rs2544386	A	T	0.2524

2	rs2544387	G	A	0.2827
2	rs12993779	T	C	0.1079
2	rs2544388	G	A	0.2822
2	rs148771995	C	G	0.01904
2	rs191510832	G	T	0.04102
2	rs139905197	T	G	0.3735
2	rs76668605	A	G	0.3447
2	rs74624697	T	G	0.2754
2	rs141248390	A	G	0.2476
2	rs6748227	C	T	0.269
2	rs6719945	A	G	0.3838
2	rs6706284	T	C	0.3667
2	rs6706290	T	C	0.3574
2	rs6706292	T	A	0.3477
2	rs143010438	T	C	0.06348
2	rs830992	A	G	0.3042
2	rs830993	A	T	0.2754
2	rs10515931	T	C	0.05811
2	rs830994	G	A	0.4658
2	rs830995	A	G	0.3477
2	rs10515930	C	G	0.06396
2	rs10490129	C	G	0.04395
2	rs77612812	A	C	0.04395
2	rs3770607	T	G	0.01904
2	rs830997	A	G	0.3364
2	rs830998	A	C	0.2173
2	rs830999	G	A	0.252
2	rs831000	T	C	0.2173

2	rs831001	T	C	0.2163
2	rs831002	T	C	0.2231
2	rs831003	G	C	0.2422
2	rs2673179	G	A	0.3105
2	rs2544372	C	T	0.2212
2	rs62173979	G	A	0.06055
2	rs7568568	C	T	0.1787
2	rs59076959	C	T	0.07178
2	rs62173981	G	A	0.4248
2	rs831004	T	C	0.3657
2	rs831005	G	A	0.4341
2	rs831006	C	G	0.3418
2	rs73037812	G	T	0.2334
2	rs831007	T	C	0.2827
2	rs831008	C	T	0.1729
2	rs831009	G	A	0.2646
2	rs831010	C	T	0.1841
2	rs72878449	G	A	0.2285
2	rs831011	A	G	0.2637
2	rs831012	C	T	0.2861
2	rs831013	T	G	0.3716
2	rs56325975	C	G	0.1338
2	rs75581025	G	A	0.06885
2	rs831014	T	G	0.1836
2	rs831015	T	C	0.3853
2	rs72878458	T	C	0.125
2	rs55679014	G	T	0.2031
2	rs58338106	T	C	0.2886

2	rs9653235	A	C	0.06641
2	rs11896551	T	C	0.07129
2	rs831016	G	C	0.4102
2	rs3770611	C	A	0.4077
2	rs3770612	G	A	0.1201
2	rs72878472	C	T	0.1616
2	rs10754970	A	G	0.2368
2	rs72878477	T	C	0.1064
2	rs2161039	T	C	0.252
2	rs831017	G	A	0.4648
2	rs16856748	A	G	0.1235
2	rs831019	T	G	0.4565
2	rs3770613	T	C	0.355
2	rs61219833	C	T	0.09521
2	rs831020	A	G	0.1929
2	rs59457398	C	T	0.09521
2	rs72878487	A	G	0.07275
2	rs62171263	A	G	0.1753
2	rs831022	C	T	0.4785
2	rs11887007	A	C	0.3472
2	rs62171264	A	G	0.01562
2	rs2229266	A	G	0.3062
2	rs16856759	G	A	0.374
2	rs2673165	T	C	0.395
2	rs13396247	A	T	0.2725
2	rs2673164	T	C	0.3965
2	rs2673163	C	T	0.1689
2	rs3770615	G	A	0.02393

2	rs2673162	T	C	0.3315
2	rs2222020	A	C	0.3652
2	rs2222019	A	C	0.3657
2	rs9287914	A	T	0.2861
2	rs2544373	T	A	0.375
2	rs2544374	G	A	0.2129
2	rs2244407	T	C	0.1694
2	rs830962	A	G	0.4658
2	rs830963	A	G	0.457
2	rs3770616	T	C	0.2632
2	rs7575260	A	G	0.2632
2	rs830964	C	T	0.4233
2	rs4667600	A	T	0.2666
2	rs3914468	G	A	0.2734
2	rs830965	A	G	0.4038
2	rs2892802	T	G	0.06738
2	rs700550	C	T	0.2036
2	rs830966	G	C	0.2593
2	rs830967	A	T	0.2041
2	rs830968	T	C	0.2041
2	rs830969	A	G	0.2075
2	rs58208595	T	C	0.01172
2	rs853988	C	A	0.2124
2	rs830970	T	C	0.2266
2	rs7600757	A	G	0.4966
2	rs830971	C	G	0.2266
2	rs830972	G	A	0.2124
2	rs12622085	G	A	0.1011

2	rs2247506	C	T	0.313
2	rs17848175	A	G	0.05078
2	rs2673170	C	G	0.4478
2	rs2673169	C	G	0.4541
2	rs80083165	C	T	0.4561
2	rs142912973	C	T	0.3677
2	rs6752012	A	C	0.4233
2	rs4638759	C	G	0.2959
2	rs7604111	A	G	0.4575
2	rs10177180	G	A	0.438
2	rs10177361	A	G	0.4365
2	rs3845730	G	A	0.4429
2	rs2544376	C	T	0.458
2	rs2544377	A	G	0.458
2	rs2673167	G	C	0.4648
2	rs2544378	T	C	0.4214
2	rs2544379	A	G	0.4214
2	rs2544380	T	G	0.3931
2	rs2544381	C	G	0.4438
2	rs10221870	A	C	0.3765
2	rs3770623	T	C	0.4336
2	rs3770624	C	A	0.436
2	rs2544383	T	A	0.4419
2	rs2544384	C	T	0.4419
2	rs861239	C	T	0.4355
2	rs2229263	C	T	0.4355
2	rs830974	C	T	0.4414
2	rs28490283	T	C	0.01318

2	rs830976	T	C	0.4365
2	rs830977	C	G	0.436
2	rs830979	A	G	0.4863
2	rs2673178	G	A	0.4409
2	rs2673177	A	G	0.4409
2	rs3845731	A	G	0.2705
2	rs13006076	G	T	0.01514
2	rs831025	A	T	0.4058
2	rs3770630	C	T	0.2583
2	rs6433115	C	T	0.2583
2	rs831027	T	C	0.08691
2	rs74505905	T	C	0.0498
2	rs831029	C	G	0.3872
2	rs78991977	G	A	0.07764
2	rs831030	T	C	0.4072
2	rs831031	G	A	0.4248
2	rs831032	A	G	0.1274
2	rs831034	T	C	0.1245
2	rs10930352	C	T	0.2759
2	rs11889511	G	C	0.2617
2	rs6751001	T	C	0.2773
2	rs60641214	T	A	0.3438
2	rs16856823	T	A	0.08105
2	rs831036	C	G	0.4307
2	rs831037	G	A	0.4424
2	rs831038	C	T	0.4424
2	rs3770636	G	T	0.08105
2	rs3770637	C	T	0.0708

2	rs3729573	T	C	0.4736
2	rs2673171	G	A	0.07568
2	rs77073020	G	A	0.1489
2	rs3821129	C	T	0.06641
2	rs2673172	G	T	0.3486
2	rs2544390	C	T	0.3486
2	rs2390793	T	C	0.2285
2	rs3770641	T	A	0.2065
2	rs6730118	G	A	0.2798
2	rs2544392	T	C	0.3862
2	rs4668134	T	A	0.08252
2	rs2389558	T	C	0.3198
2	rs4668135	A	C	0.06055
2	rs13002515	T	A	0.1382
2	rs13003297	C	G	0.1377
2	rs6713072	T	C	0.3164
2	rs1990842	C	A	0.2051
2	rs12614394	G	A	0.1372
2	rs10199321	T	C	0.2095
2	rs10199676	T	G	0.21
2	rs16856840	A	G	0.06836
2	rs2673151	T	C	0.1406
2	rs13017888	T	C	0.1377
2	rs13017872	G	A	0.1406
2	rs13017879	T	A	0.1377
2	rs6721930	C	G	0.2769
2	rs2389557	A	G	0.4673
2	rs830943	A	G	0.1465

2	rs12995288	G	A	0.1362
2	rs34038476	T	A	0.1372
2	rs16856843	A	G	0.0791
2	rs4668136	T	C	0.3218
2	rs3845732	C	T	0.438
2	rs12692895	T	C	0.1279
2	rs3815679	T	C	0.04736
2	rs3815680	G	T	0.08008
2	rs2161038	C	G	0.1382
2	**rs3755166**	**A**	**G**	**0.3018**
2	rs6755801	T	A	0.2974
2	rs12612683	C	T	0.1323
2	rs830952	C	A	0.4468
2	rs700552	C	G	0.4971
2	rs58599996	A	C	0.1782
2	rs830954	C	T	0.4932
2	rs830955	A	C	0.4927
2	rs10167272	C	T	0.1821
2	rs148386284	T	G	0.2554
2	rs112277758	C	G	0.2632
2	rs140297819	G	C	0.1743
2	rs145088245	C	T	0.05273
2	rs2544371	G	A	0.4243
2	rs2673166	C	A	0.2847
2	rs61707661	T	C	0.3359
2	rs143130711	C	T	0.04346
2	rs13026171	T	C	0.2573
2	rs2673159	C	T	0.4395

2	rs13002827	C	T	0.07715
2	rs12470146	A	C	0.008789
2	rs62171289	A	T	0.356
2	rs12616998	C	T	0.4062
2	rs12613663	T	G	0.4062
2	rs78893940	C	T	0.06396
2	rs12692897	G	A	0.251
2	rs12692898	G	A	0.4062
2	rs1344	G	A	0.4058
2	rs1356057	C	G	0.4048
2	rs1356056	C	T	0.4043
2	rs13423674	G	A	0.4043
2	rs12692899	A	C	0.4038
2	rs12692900	G	A	0.249
2	rs12622978	C	A	0.1562
2	rs7567342	C	T	0.4048
2	rs11900616	A	T	0.4058
2	rs11895060	A	C	0.4111
2	rs4667601	A	G	0.03027
2	rs4566330	G	A	0.4912
2	rs34155127	G	A	0.05811
2	rs4668139	G	A	0.05859
2	rs1606797	C	A	0.4824
2	rs6721866	T	C	0.1528
2	rs4338933	T	C	0.2798
2	rs12463500	G	A	0.1343
2	rs34996026	T	C	0.1353
2	rs4668141	C	T	0.4478

12	rs11168262	T	C	0.1206
12	rs12721364	A	G	0.03271
12	rs7965281	G	A	0.375
12	rs10783215	C	T	0.4014
12	rs7968585	C	T	0.3965
12	rs2525046	T	C	0.251
12	rs2408875	T	G	0.4976
12	rs11574143	T	C	0.08789
12	rs2853563	T	C	0.1597
12	rs2853562	T	A	0.3052
12	rs9729	G	T	0.4292
12	rs3847987	A	C	0.07373
12	rs739837	G	T	0.4331
12	**rs731236**	**G**	**A**	**0.2803**
12	**rs7975232**	**C**	**A**	**0.3779**
12	rs11574114	T	C	0.1587
12	rs11574113	G	C	0.08398
12	rs10875692	T	C	0.005371
12	rs757343	T	C	0.07373
12	**rs1544410**	**T**	**C**	**0.2944**
12	rs55748765	T	C	0.3281
12	rs10783217	A	G	0.2197
12	rs2238141	C	T	0.4238
12	rs2525044	A	G	0.2222
12	rs7139204	G	C	0.4233
12	rs12314197	G	A	0.2051
12	rs7962898	T	C	0.3623
12	rs58789572	T	C	0.2007

12	rs7963776	G	A	0.4238
12	rs4760732	C	T	0.4751
12	rs4760733	A	G	0.4502
12	rs7967152	A	C	0.3979
12	rs2239185	G	A	0.4233
12	rs2239184	G	A	0.3809
12	rs7971418	C	A	0.4512
12	rs7975128	A	G	0.2798
12	rs11168264	G	A	0.2129
12	rs113322950	C	T	0.2471
12	rs7296204	G	A	0.2393
12	rs7316602	C	T	0.271
12	rs11168265	T	C	0.2832
12	rs7305032	G	A	0.2886
12	rs11168266	C	T	0.4111
12	rs11168267	A	G	0.07227
12	rs11168268	G	A	0.3589
12	rs2238140	G	A	0.4907
12	rs2248098	A	G	0.4937
12	rs2283344	T	C	0.3208
12	rs12370156	C	T	0.4883
12	rs987849	G	A	0.2529
12	rs2283343	A	G	0.4668
12	rs2239182	T	C	0.4058
12	rs2107301	A	G	0.166
12	rs2283342	G	A	0.02783
12	rs2239181	C	A	0.1323
12	rs2239180	G	C	0.1318

12	rs2238139	G	A	0.2378
12	rs1540339	T	C	0.228
12	rs2239179	C	T	0.334
12	rs12717991	T	C	0.3091
12	rs7965360	A	G	0.3647
12	rs7968852	A	G	0.292
12	rs7308350	A	C	0.3174
12	rs12721370	A	C	0.07422
12	rs886441	G	A	0.4111
12	rs1808208	G	A	0.2461
12	rs73109883	A	G	0.1152
12	rs2189480	T	G	0.3589
12	rs2238138	A	G	0.2271
12	rs2238137	T	C	0.03711
12	rs12721395	A	T	0.1826
12	rs59707231	T	A	0.1826
12	rs3819545	G	A	0.2583
12	rs117572434	C	T	0.1895
12	rs12721396	A	G	0.228
12	rs3782905	C	G	0.2192
12	rs61919100	G	C	0.04102
12	rs113270938	T	C	0.04102
12	rs7311713	T	G	0.231
12	rs11168274	T	C	0.3232
12	rs181665806	T	G	0.1226
12	rs12721397	G	A	0.2295
12	rs2239186	G	A	0.05566
12	rs10875693	A	T	0.167

12	rs7974353	T	C	0.1313
12	rs61919101	G	A	0.1011
12	rs7974708	C	T	0.1997
12	rs6580642	T	C	0.1338
12	rs11168275	C	T	0.3262
12	rs11574050	A	G	0.06104
12	rs10783218	A	G	0.1318
12	rs2228570	A	G	0.2188
12	rs2408876	C	T	0.4482
12	rs2254210	A	G	0.3237
12	rs2408877	T	A	0.08984
12	rs7297462	C	T	0.07568
12	rs12721373	A	T	0.01953
12	rs11574044	C	A	0.2021
12	rs11574042	G	C	0.1255
12	rs2238136	T	C	0.08545
12	rs1989969	A	G	0.4316
12	rs2238135	G	C	0.293
12	rs2853564	G	A	0.1338
12	rs7965266	T	A	0.1313
12	rs7965274	T	C	0.1313
12	rs12321826	T	C	0.09668
12	rs7979131	G	T	0.1313
12	rs4760648	C	T	0.4565
12	rs4760649	A	G	0.1978
12	rs2853561	T	C	0.332
12	rs10875694	A	T	0.09375
12	rs12298585	G	C	0.127

12	rs11168283	T	C	0.1875
12	rs2853559	A	G	0.1909
12	rs12721375	A	G	0.02344
12	rs11168284	G	A	0.4355
12	rs7965943	T	G	0.3882
12	rs2853566	G	A	0.189
12	rs2853565	G	A	0.2646
12	rs11168286	A	G	0.03467
12	rs4760650	T	G	0.4883
12	rs7966244	T	A	0.417
12	rs12302580	C	G	0.2158
12	rs3922882	G	C	0.1611
12	rs11168287	G	A	0.3042
12	rs4328262	G	T	0.3232
12	rs4334089	G	A	0.4009
12	rs4237855	G	A	0.2612
12	rs5013378	G	A	0.4985
12	rs4341603	G	T	0.4912
12	rs11574027	A	C	0.01318
12	rs7965397	G	T	0.1143
12	rs3890734	A	G	0.1479
12	rs3890733	T	C	0.1489
12	rs111336890	C	T	0.1196
12	rs7302235	C	T	0.4829
12	rs58379944	G	A	0.09717
12	rs10875695	A	C	0.4829
12	rs11168292	G	C	0.1479
12	rs11168293	T	G	0.1479

12	rs4760655	G	A	0.08105
12	rs7136534	T	C	0.09229
12	rs12581281	T	C	0.03174
12	rs10783219	T	A	0.08008
12	rs10083198	T	C	0.2524
12	rs7299460	C	T	0.25
12	rs4760658	G	A	0.1514
12	rs7979360	G	A	0.4434
12	rs11574012	G	A	0.03369
12	rs4516035	C	T	0.08203
12	rs7139166	G	C	0.08203
12	rs10875696	T	G	0.09082
12	rs11614332	A	G	0.09277
12	**rs11568820**	**C**	**T**	**0.21**
12	rs11168297	A	G	0.08447
12	rs4760603	T	A	0.08301
12	rs7310552	G	A	0.08398
12	rs4411327	C	T	0.4399
12	rs7975847	T	C	0.4404
12	rs7976091	C	T	0.2104
12	rs10875697	T	A	0.3535

Note: Bolded SNPs are the ones that were selected for haplotype analysis.

Table S2. Key findings from single SNP analysis with incident and prevalent MetS outcomes, overall and stratified by sex.

**********Incident MetS**********

Overall:

SNPrs11898106_g	2.292095	.7141345	2.66	0.008	1.244597	4.221205
SNPrs830969_a	2.445877	.8414834	2.60	0.009	1.246194	4.800465
SNPrs853988_c	2.591791	.9185341	2.69	0.007	1.293996	5.19119
SNPrs830972_g	2.591791	.9185341	2.69	0.007	1.293996	5.19119
SNPrs17848175_a	3.519254	1.57947	2.80	0.005	1.46024	8.481584
SNPrs831032_a	3.045186	1.1736	2.89	0.004	1.430753	6.481311
SNPrs831034_t	3.106713	1.200571	2.93	0.003	1.456664	6.625869
SNPrs3815679_t	4.828003	2.819711	2.70	0.007	1.536873	15.16691
SNPrs148386284_t	**2.626265**	**.796895**	**3.18**	**0.001**	**1.448959**	**4.760155**
SNPrs112277758_c	2.568595	.7721236	3.14	0.002	1.425027	4.629863
SNPrs2544371_g	.4211706	.1372794	-2.65	0.008	.2223368	.7978198
SNPrs13026171_t	2.502543	.7536467	3.05	0.002	1.386885	4.515678
SNPrs2673159_c	.457887	.1367192	-2.62	0.009	.2550355	.8220839
SNPrs12692897_g	2.58272	.8294801	2.95	0.003	1.376261	4.846785
SNPrs12692900_g	2.379948	.7512276	2.75	0.006	1.281996	4.418228

__Men__

SNPrs75950705_a	154.1337	262.3659	2.96	0.003	5.482585	4333.213
SNPrs10204688_c	31.90083	47.09618	2.35	0.019	1.766634	576.046
SNPrs2024480_a	31.90083	47.09618	2.35	0.019	1.766634	576.046
SNPrs16856573_t	.0067755	.0124439	-2.72	0.007	.0001852	.2478918
SNPrs2302696_t	29.30606	38.48466	2.57	0.010	2.2344	384.3738
SNPrs2052297_c	203.4858	398.0846	2.72	0.007	4.398515	9413.737
SNPrs10190812_t	.0259778	.0401426	-2.36	0.018	.0012568	.5369498
SNPrs11897009_t	.0259778	.0401426	-2.36	0.018	.0012568	.5369498
SNPrs4668128_g	18.97355	22.73207	2.46	0.014	1.812717	198.5944
SNPrs2239594_c	23.1881	30.39854	2.40	0.016	1.775737	302.797
SNPrs6724600_g	155.2049	295.0959	2.65	0.008	3.736706	6446.467
SNPrs2673175_t	.0001106	.000427	-2.36	0.018	5.74e-08	.2133398
SNPrs6706284_t	.028124	.0395078	-2.54	0.011	.001792	.4413881
SNPrs6706292_t	.003089	.0075579	-2.36	0.018	.0000255	.3736632
SNPrs830994_g	.0187236	.0308215	-2.42	0.016	.0007434	.471608
SNPrs2161039_t	1008.545	2775.499	2.51	0.012	4.583552	221915.8
SNPrs62171263_a	1454.726	4152.921	2.55	0.011	5.404916	391537.5
SNPrs2222020_a	.0370027	.0461541	-2.64	0.008	.0032101	.4265327
SNPrs2222019_a	.0370027	.0461541	-2.64	0.008	.0032101	.4265327
SNPrs9287914_a	17.46258	20.51715	2.43	0.015	1.745879	174.6637
SNPrs2544374_g	.0639913	.0742439	-2.37	0.018	.0065848	.6218727

SNPrs2544373_t | .0370031 .0461548 -2.64 0.008 .0032101 .4265411
SNPrs4667600_a | 10.71159 10.71763 2.37 0.018 1.507202 76.1265
SNPrs3914468_g | 30.96926 41.30342 2.57 0.010 2.268251 422.8347
SNPrs4668135_a | 133.5783 261.5591 2.50 0.012 2.877411 6201.117
SNPrs3815679_t | 548.6712 1410.554 2.45 0.014 3.556284 84650.17
SNPrs58599996_a | 125.8762 210.2276 2.90 0.004 4.768038 3323.131
SNPrs112277758_c | 12.85109 13.90295 2.36 0.018 1.541941 107.1056
SNPrs140297819_g | 125.8762 210.2276 2.90 0.004 4.768038 3323.131
SNPrs13026171_t | 12.851 13.90278 2.36 0.018 1.541947 107.1037
SNPrs12692897_g | 32.10611 47.16342 2.36 0.018 1.803784 571.4666
SNPrs12692900_g | 32.10611 47.16342 2.36 0.018 1.803784 571.4666
SNPrs12622978_c | 1844.766 5057.653 2.74 0.006 8.555938 397754.4

__Women__
SNPrs2024481_a | .1457287 .0930145 -3.02 0.003 .0417107 .5091465
SNPrs2229265_t | .2081133 .1227268 -2.66 0.008 .0655144 .661094
SNPrs56325975_c | .0782228 .0773183 -2.58 0.010 .0112713 .5428659
SNPrs13396247_a | .1027846 .0864311 -2.71 0.007 .0197768 .5341952
SNPrs9287914_a | .1486556 .1058031 -2.68 0.007 .0368428 .5998044
SNPrs3770616_t | .1038038 .0864259 -2.72 0.007 .0203008 .5307793
SNPrs7575260_a | .1038038 .0864259 -2.72 0.007 .0203008 .5307793
SNPrs4667600_a | .1839065 .1257039 -2.48 0.013 .0481707 .7021194
SNPrs3914468_g | .159003 .1116665 -2.62 0.009 .0401434 .6297917
SNPrs2892802_t | 3.88091 2.219388 2.37 0.018 1.265186 11.90455
SNPrs700550_c | 4.003154 1.974007 2.81 0.005 1.522873 10.52303
SNPrs830966_g | 4.281696 1.896411 3.28 0.001 1.797253 10.20052
SNPrs830967_a | 3.993804 1.968272 2.81 0.005 1.520155 10.49266
SNPrs830968_t | 3.993804 1.968272 2.81 0.005 1.520155 10.49266
SNPrs830969_a | 3.935537 1.938095 2.78 0.005 1.499067 10.33206
SNPrs831030_t | .3433465 .1565591 -2.34 0.019 .1404759 .8391962
SNPrs2673151_t | 5.17998 3.171477 2.69 0.007 1.560178 17.19815
SNPrs830943_a | 4.773296 2.569862 2.90 0.004 1.661674 13.71169
SNPrs2107301_a | 3.856908 1.789459 2.91 0.004 1.55351 9.575567
SNPrs2239181_c | 3.554051 1.78874 2.52 0.012 1.32531 9.530814
SNPrs2239180_g | 3.554051 1.78874 2.52 0.012 1.32531 9.530814
SNPrs12721397_g | 4.722825 2.473695 2.96 0.003 1.691859 13.18376
SNPrs2238135_g | 2.709058 1.142603 2.36 0.018 1.185239 6.191997
SNPrs4516035_c | .0003625 .0007642 -3.76 0.000 5.82e-06 .0225664
SNPrs7139166_g | .0003625 .0007642 -3.76 0.000 5.82e-06 .0225664
SNPrs10875696_t | .0003674 .0007739 -3.76 0.000 5.92e-06 .0228039
SNPrs11614332_a | .0003694 .000779 -3.75 0.000 5.92e-06 .0230531
SNPrs11568820_c | .1061112 .080666 -2.95 0.003 .0239153 .470811
SNPrs11168297_a | .0003625 .0007642 -3.76 0.000 5.82e-06 .0225664
SNPrs7310552_g | .0003625 .0007642 -3.76 0.000 5.82e-06 .0225664
SNPrs7976091_c | .0598771 .0538288 -3.13 0.002 .0102811 .3487228

**********Baseline MetS**********

Overall:

SNPrs2268368_t	.6272605	.1115087	-2.62	0.009	.4427199	.888724
SNPrs2268366_a	.6272605	.1115087	-2.62	0.009	.4427199	.888724

Men:

SNPrs11674531_g	2.07313	.6380819	2.37	0.018	1.134065	3.789789
SNPrs17848195_a	.3748364	.1536393	-2.39	0.017	.1678604	.8370191
SNPrs2673163_c	2.291486	.7618774	2.49	0.013	1.194285	4.396694
SNPrs2244407_t	2.291486	.7618774	2.49	0.013	1.194285	4.396694
SNPrs2673166_c	.4201989	.1413911	-2.58	0.010	.2172888	.8125918
SNPrs13002827_c	3.755142	1.699488	2.92	0.003	1.546653	9.117168
SNPrs4566330_g	2.051286	.5506439	2.68	0.007	1.21208	3.471534
SNPrs34155127_g	3.813479	2.059483	2.48	0.013	1.323204	10.99046
SNPrs34996026_t	2.837031	1.127943	2.62	0.009	1.301501	6.184203
SNPrs2239182_t	.4611191	.1358182	-2.63	0.009	.2588809	.8213463
SNPrs7965266_t	2.3329	.8448625	2.34	0.019	1.147182	4.744165
SNPrs7965274_t	2.3329	.8448625	2.34	0.019	1.147182	4.744165
SNPrs7979131_g	2.3329	.8448625	2.34	0.019	1.147182	4.744165
SNPrs2853566_g	2.378857	.748435	2.75	0.006	1.283996	4.407304
SNPrs2853565_g	2.700805	.8628076	3.11	0.002	1.443995	5.051504
SNPrs3922882_g	2.512153	.9136143	2.53	0.011	1.231637	5.124001

Women:

SNPrs2268368_t	.5632227	.1294154	-2.50	0.012	.3589996	.8836215
SNPrs2268366_a	.5632227	.1294154	-2.50	0.012	.3589996	.8836215
SNPrs11902433_c	1.813431	.434342	2.49	0.013	1.134035	2.899851
SNPrs34951037_a	1.74467	.4068454	2.39	0.017	1.104635	2.755547
SNPrs3821127_a	1.840489	.4462228	2.52	0.012	1.144356	2.960092
SNPrs6752778_a	1.723875	.3904727	2.40	0.016	1.105863	2.687264
SNPrs2229267_a	1.760211	.3855984	2.58	0.010	1.14577	2.704158
SNPrs1989969_a	1.756767	.412795	2.40	0.016	1.108418	2.784355

**********Follow-up MetS**********

********Overall**********

SNPrs11574044_c	.4781762	.1113382	-3.17	0.002	.3029666	.7547117
SNPrs4760603_t	2.002399	.5215423	2.67	0.008	1.201843	3.336211

********Men**********

SNPrs146901930_a	.1370364	.1142064	-2.38	0.017	.0267573	.7018253
SNPrs17848195_a	.3190816	.1515506	-2.41	0.016	.1257813	.8094452
SNPrs73971315_g	.3646399	.1478522	-2.49	0.013	.1647114	.8072439
SNPrs2673175_t	.2401759	.1395053	-2.46	0.014	.0769329	.7498022
SNPrs2544386_a	.2211334	.1100727	-3.03	0.002	.0833595	.5866158
SNPrs141248390_a	.2220275	.1105593	-3.02	0.003	.0836658	.5892035

SNPrs830994_g	.3883239	.1400447	-2.62	0.009	.1915216	.7873549
SNPrs830995_a	.3682697	.1397929	-2.63	0.008	.1750069	.7749555
SNPrs830998_a	.3009102	.1427092	-2.53	0.011	.1187811	.7623009
SNPrs831000_t	.3009102	.1427092	-2.53	0.011	.1187811	.7623009
SNPrs831001_t	.3009102	.1427092	-2.53	0.011	.1187811	.7623009
SNPrs831002_t	.2931144	.1386247	-2.59	0.009	.1160038	.7406312
SNPrs2544372_c	.2983195	.1410801	-2.56	0.011	.1180687	.7537521
SNPrs831027_t	3.567771	1.587104	2.86	0.004	1.491916	8.531971
SNPrs78991977_g	4.066832	1.884048	3.03	0.002	1.640283	10.08309
SNPrs16856823_t	2.920439	1.263456	2.48	0.013	1.250825	6.818669
SNPrs3770636_g	2.920439	1.263456	2.48	0.013	1.250825	6.818669
SNPrs4566330_g	2.145472	.6391648	2.56	0.010	1.196571	3.846867
SNPrs34155127_g	5.893035	3.532662	2.96	0.003	1.820012	19.08111
SNPrs4760648_c	2.492837	.8844024	2.57	0.010	1.243675	4.996674
SNPrs2853566_g	2.292185	.796091	2.39	0.017	1.160437	4.527699

********<u>**Women**</u>**********

SNPrs2673165_t	1.757246	.3646304	2.72	0.007	1.170057	2.639111
SNPrs13396247_a	.5030988	.1317353	-2.62	0.009	.3011397	.8405014
SNPrs2673164_t	1.728496	.3595509	2.63	0.009	1.149759	2.598544
SNPrs9287914_a	.5643848	.1370892	-2.35	0.019	.3506052	.9085155
SNPrs2544373_t	1.630716	.3299878	2.42	0.016	1.09681	2.424518
SNPrs700550_c	2.024985	.5177484	2.76	0.006	1.226836	3.34239
SNPrs830966_g	1.951917	.4499172	2.90	0.004	1.242394	3.066645
SNPrs830967_a	2.01782	.5160316	2.75	0.006	1.222358	3.330936
SNPrs830968_t	2.01782	.5160316	2.75	0.006	1.222358	3.330936
SNPrs830969_a	1.902251	.4857009	2.52	0.012	1.15327	3.137652
SNPrs853988_c	2.031602	.5290717	2.72	0.006	1.219461	3.384616
SNPrs830972_g	2.031602	.5290717	2.72	0.006	1.219461	3.384616
SNPrs11574114_t	.4187679	.151039	-2.41	0.016	.2065221	.8491417
SNPrs2107301_a	2.032922	.5675101	2.54	0.011	1.17625	3.513517

Note: Criterion for reporting results: $p<0.01$ (overall) and $p<0.02$ per gender group: Criterion for noteworthy results> $p\leq 0.001$ (bolded).