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## Gene-environment interactions and obesity traits among postmenopausal African-American and Hispanic women in the Women's Health Initiative SHARe Study

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### Abstract

Genome-wide association studies of obesity measures have identified associations with single nucleotide polymorphisms (SNPs). However, no large-scale evaluation of gene-environment interactions has been performed. We conducted a search of gene-environment (G×E) interactions in post-menopausal African-American and Hispanic women from the Women's Health Initiative SNP Health Association Resource GWAS study. Single SNP linear regression on body mass index (BMI) and waist-to-hip circumference ratio (WHR) adjusted for multidimensional-scaling-derived axes of ancestry and age was run in race-stratified data with 871,512 SNPs available from African-Americans (N=8,203) and 786,776 SNPs from Hispanics (N=3,484). Tests of G×E interaction at all SNPs for recreational physical activity (met-hrs/wk), dietary energy intake (kcal/day), alcohol intake (categorical), cigarette smoking years, and cigarette smoking (ever vs. never) were run in African-Americans and Hispanics adjusted for ancestry and age at interview, followed by meta-analysis of G×E interaction terms. The strongest evidence for concordant G×E interactions in African-Americans and Hispanics was for smoking and marker rs10133840 (Q statistic  $P=0.70$ ,  $\beta=-0.01$ ,  $P=3.81\times 10^{-7}$ ) with BMI as the outcome. The strongest evidence for G×E interaction within a cohort was in African-Americans with WHR as outcome for dietary energy intake and rs9557704 (SNP×kcal =  $-0.04$ ,  $P=2.17\times 10^{-7}$ ). No results exceeded the Bonferroni-corrected statistical significance threshold.

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## Keywords

BMI; WHR; genetic epidemiology; disparity; obesity; GWAS

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## INTRODUCTION

Globally, the prevalence of obese (body mass index (BMI)  $\geq 30$ ) and overweight (BMI  $\geq 25$ ) adults (persons with age  $\geq 15$ y) has increased to approximately 1.6 billion individuals worldwide according to WHO estimates (2009). The public health impact of obesity is substantial, since the condition is associated with increased risks for several common comorbidities, including type 2 diabetes, cardiovascular disease, dyslipidemia, hypertension, sleep apnea, and several forms of cancer including postmenopausal breast cancer (Field et al., 2001; Must et al., 1999). As a result, the obesity epidemic has become major a global public health problem and economic burden.

Multiple lines of evidence indicate that a large proportion of obesity risk is mediated by genetic factors, with studies estimating that 40–90% of human population variation of BMI is due to genetic risk factors (Hjelmborg et al., 2008; Maes et al., 1997; Wardle et al., 2008). Over the last few years, several genome wide association studies (GWAS) have succeeded in identifying novel reproducible associations in candidate genes, although these appear to explain only a small proportion of obesity risk. Several of these genes are expressed or are known to function in the central nervous system (CNS) (Frayling et al., 2007; Loos et al., 2008; Meyre et al., 2009; Speliotes et al., 2010; Thorleifsson et al., 2009; Willer et al., 2009) supporting their role in regulating food intake and metabolism.

In the US, the obesity epidemic disproportionately affects ethnic minorities, including African-Americans (Ogden et al., 2006). Hispanic and African-American (non-Hispanic) adults in the U.S. are overweight and obese more often than European-American (non-Hispanic) adults (Flegal et al., 2010). For example, about half of non-Hispanic African-American and Hispanic women in their forties and fifties are obese, whereas only 36 percent of same-age European American women are obese (Flegal et al., 2010). The causes of the excess are poorly understood, but may be related to behavioral, environmental and genetic risk factors (Ogden et al., 2006). Although understanding the way in which genotype and environmental/behavioral risk factors interact may offer insights into modifiable behavioral changes that could reduce obesity risk, few studies have been performed to evaluate those phenomena (Hetherington and Cecil, 2010).

In the present study, we examined G×E interactions between single nucleotide polymorphisms (SNPs) genotyped in multi-ethnic GWAS that included African-American and Hispanic postmenopausal women in the Women's Health Initiative (WHI)-Observational Study and the WHI-Clinical Trial. Our primary outcomes of interest were BMI and waist-to-hip ratio (WHR) and we focused on environmental/behavioral risk factors known to be associated with body weight, including recreational physical activity levels, total dietary energy intake, cigarette smoking, and alcohol intake.

## MATERIALS AND METHODS

### Study Population

The data used in this study were obtained from African-American and Hispanic women genotyped as part of the WHI-Observational Study (WHI-OS) and randomized clinical trial (WHI-CT) SNP Health Associated Resource (SHARe) GWAS of minority women. The WHI-OS is a prospective study that recruited 93,676 postmenopausal women ages 50–79

across 40 clinical centers in the United States between October 1, 1993 and December 31, 1998 who were not participating in the WHI-CT (1998;2009; Curb et al., 2003; Hays et al., 2003; Langer et al., 2003). The original protocol followed women until 2005; the women were then invited to participate in the WHI-OS Extension Study for continued follow-up through 2010. Women were excluded from participating in the WHI-OS if they were currently participating in an existing randomized trial, had medical complications that predicted survival at less than 3 years, or conditions that prevented study participation or adherence (1998;2009; Curb et al., 2003; Hays et al., 2003; Langer et al., 2003). The WHI-CT enrolled 68,132 postmenopausal women between 50–79 years of age from 1993–1998 and grouped women into trials focused on three prevention strategies: hormone therapy, dietary modification, and calcium/vitamin D (Carty et al., 2011; Manson et al., 2007; Neuhouser et al., 2009). Within the cohort of women that include the WHI-OS and WHI-CT we conducted a retrospective case-control study of African-American and Hispanic women who provided blood samples and were subsequently genotyped as part of the WHI-OS SHARe GWAS for minority women.

Information regarding demographics, clinical, behavioral characteristics, medical history, lifestyle/behavioral factors, and details of physical activity, among other risk factors, were obtained by standardized self-administered questionnaires at baseline. Measurements for weight, height, waist, and hip were ascertained during a baseline physical examination conducted by WHI. Protocols and ascertainment for WHI have been previously described (1998;2009; Curb et al., 2003; Hays et al., 2003; Langer et al., 2003). Variables examined in this study include: age at baseline interview (years [y]), BMI ( $\text{kg}/\text{m}^2$ ), WHR measurements, recreational physical activity (met-hrs/week), total dietary energy intake (kcal/day), cigarette smoking (y), cigarette smoking (ever vs. never), and alcohol intake (categorical, nondrinkers [referent], past drinkers, <1 drink/month, <1 drink/week, 1 to 7 drinks/week, 7 drinks/week).

The primary outcomes for this study were BMI and WHR, as measured in baseline interviews. Among the 12,008 women who were genotyped as part of the WHI SHARe GWAS dataset 8,400 African-American women and 3,587 Hispanic women had either BMI or measurements of WHR from the baseline interview.

### Genotyping

The Affymetrix Human SNP Array 6.0 (Affymetrix®, Inc Santa Clara, CA) was used for genome wide SNP genotyping. Genomic DNA was quantitated via an ND-8000 spectrophotometer and DNA quality was evaluated via gel electrophoresis. The genomic DNA samples were processed according to standard Affymetrix procedures for processing of the assay. The data were processed for genotype calling using the Affymetrix® Genotypic Console software using the Birdseed calling algorithm version 2.0 (Affymetrix®, Inc., Santa Clara, CA) (Korn et al., 2008).

### Quality Control

Data on 909,622 SNPs and 12,008 individuals were available prior to implementation of quality control. No individuals were removed after excluding individuals with low genotyping efficiency (<95%). 251 individuals were removed after kinship estimates identified related individuals using identity-by-descent sharing from a random selection of 100,000 autosomal SNPs. When a pair of related individuals was identified, only one member (parent or sibling) of the family was included, with priority given to parent over offspring. 11,757 unrelated women remained in the final dataset, and among these 11,687 had baseline measures of BMI.

All SNPs were tested for deviation from Hardy-Weinberg equilibrium (HWE) using PLINK software, stratified by race (Purcell et al., 2007). We excluded SNPs with HWE  $P < 10^{-6}$ , dropping 17,562 SNPs in African-Americans and 8,571 SNPs in Hispanics. Markers with low genotyping efficiency (<95%) were also excluded, 6,020 SNPs in African-Americans and 6,967 SNPs in Hispanics. SNPs with a MAF<0.01 were also excluded, dropping 14,528 SNPs in African-Americans and 47,845 SNPs in Hispanics. Finally, those SNPs that did not map to a chromosomal position were excluded. This resulted in the removal of 62 SNPs in African-American and 57 SNPs in Hispanic women. Only SNPs with a MAF  $\geq 0.05$  were considered to maintain stability of effect estimates and statistical validity for hypothesis tests at interaction terms, resulting in the removal of 84,674 SNPs in African-Americans and 130,820 SNPs in Hispanics and a total of 786,776 SNPs in African-Americans and 706,791 SNPs in Hispanics available for analysis. Quality control procedures are presented in Supplemental Figure 1.

In order to assess population stratification among African-American and Hispanic samples multi-dimensional scaling (MDS) was employed using PLINK software (Purcell et al., 2007) to estimate continuous axes of ancestry. The top two MDS components were extracted among African-American and Hispanic groups individually and used as covariates in the statistical models to test for association (Supplemental Figure 2).

Quantitative and ordinal variables were examined for normality, skewness, and kurtosis by performing the Shapiro-Wilk test of normality, visual inspection of normal quantile and histogram plots, and kurtosis and skewness summary statistics available from analysis in the Stata statistical software package, version 11 (StataCorp, College Station, TX, USA). Quantile-quantile (QQ) plots for each gene-environment interaction were examined and are provided in Supplemental Figures 3–4.

## Statistical Analyses

The associations between each genetic marker and BMI, and WHR adjusted for BMI were assessed using linear regression stratified by race while adjusting for age and MDS-derived axes of ancestry using PLINK (Purcell et al., 2007). Demographic variables were analyzed with two-sample Wilcoxon rank-sum tests to compare between racial groups when variables were continuous, and Chi-squared tests were used for binary variables. Analyses of demographic data and transformations were conducted using Stata 11.

The relationship between BMI and WHR and environmental risk factors related to obesity were investigated separately for BMI and WHR as outcomes. Each factor was regressed separately on BMI and WHR adjusted for BMI in a linear regression model while adjusting for age. A robust measure of standard error was used in these regression analyses. BMI and WHR were not normally distributed; therefore we performed a Box-Cox transformation for both BMI and WHR. The normality of regression residuals was verified to evaluate the modeling approach. Histograms of the BMI and WHR distributions are provided in Supplemental Figure 5A and 5B and Supplemental Figure 6A and 6B. Dietary energy was also non-normally distributed and had a highly right-skewed distribution; after evaluating transformations, a log transformation was used.

For the G×E interaction investigation of BMI and WHR adjusted for BMI, we also included adjustments for MDS-derived axes of ancestry, age at interview, and terms for the environmental variable and additively encoded SNP genotypes in linear regression models. We followed up G×E interaction analyses with random-effects meta-analysis between African-American and Hispanic results using PLINK (Purcell et al., 2007), because underlying differences in population histories, correlations among SNPs, and modifiers may lead to heterogeneity in interaction effects. All *P*-values are two-sided.

The most significant gene-environment interactions in AAAfrican-American and Hispanic subjects with BMI as outcome were also evaluated using logistic regression subdividing BMI into strata (BMI<25.0 [referent], 25.0–29.9, 30.0–34.9, and 35.0 kg/m<sup>2</sup>) and evaluating each category vs. BMI<25.0 kg/m<sup>2</sup> as the outcome to estimate the change in risk of overweight, obesity, and severe obesity, respectively. These models were adjusted for age at interview and ancestry.

## RESULTS

### Demographic data

This study included 8,203 African-American and 3,484 Hispanic female participants (Table 1). African-Americans had a higher BMI overall (mean=31.0 kg/m<sup>2</sup>±6.4) and proportion of obese (BMI ≥30.0 kg/m<sup>2</sup>) individuals (50.3%) compared to Hispanics (mean BMI=28.9±5.6 kg/m<sup>2</sup>, 35.9% obese) ( $P<10^{-4}$ ). However, WHR was higher overall among Hispanics (mean=0.82±0.07) than African-Americans (mean=0.79±0.59) ( $P<10^{-4}$ ). African-Americans reported approximately 14.5% more individuals who had ever smoked cigarettes when compared to Hispanics (37.6% “ever” smokers) ( $P<10^{-4}$ ). African-Americans also reported more years of cigarette smoking (mean = 1.93 years) when compared to Hispanics (mean=1.14y) ( $P<10^{-4}$ ). Hispanics reported higher mean recreational physical activity hrs/week overall, total dietary energy intake, and alcohol intake (servings [12 ounces]/week).

### Environmental/behavioral risk factors and BMI and WHR

Table 2 summarizes the association between BMI and WHR and other candidate environmental/behavioral risk factors. We examined age at interview, years of cigarette smoking, “ever” vs. “never” cigarette smoking, recreational physical activity, total dietary energy intake, and alcohol intake (categorically coded with nondrinker as referent). We observed statistically significant associations with BMI decreasing and WHR increasing with age at interview. BMI and WHR were inversely associated with recreational physical activity and alcohol intake in African-Americans and Hispanics. Increasing dietary energy intake significantly increased both WHR and BMI in African-Americans and Hispanics. We also observed decreases of BMI with years of cigarette smoking among African-Americans, but not Hispanics where they were weakly positively correlated, but without statistically significant association (Beta=0.001, 95% CI [-0.02–0.02],  $P=0.953$ ). We also observed significant increases in WHR with years of smoking in African-Americans and Hispanics. All evaluated factors except recreational physical activity and alcohol intake increased either BMI or WHR with greater exposure.

### Gene-environment interactions

Potential interactions between each additively modeled genetic marker and continuous candidate obesity risk factors were examined within each racial group. The most statistically significant result from each set of tests for the transformed outcomes is provided in Table 3 for African-Americans and Table 4 for Hispanics. In order to facilitate interpretation of p values untransformed Betas are provided in Supplemental Tables 1 and 2. Summaries of single locus tests of association for SNPs highlighted for G×E interactions are provided in Supplemental Tables 3–4. We also present estimates of risk modification for other featured models of G×E interactions in Supplemental Table 5.

### BMI Outcome

The strongest gene by environment interaction with BMI as outcome among African-Americans was for the interaction between rs7350721 and cigarette smoking (years) (Beta<sub>interaction</sub>=0.41, 95% CI [0.25,0.58];  $P=5.97\times 10^{-7}$ ). This SNP was not located within a

gene but was between *LOC645687* and the gene pellino homolog 2 (*PELI2*). This SNP also had the strongest gene– “ever” vs. “never” cigarette smoking interaction with BMI ( $\text{Beta}_{\text{interaction}} = -0.02$ , 95% CI [0.01, 0.02];  $P = 3.90 \times 10^{-6}$ ). Among the strongest gene by environment interactions among African-Americans with BMI as outcome, only one interaction involved a SNP located within a gene—rs4549702. The gene was contactin associated protein-like 2 (*CNTNAP2*) and interacted with dietary energy intake ( $\text{Beta}_{\text{interaction}} = -0.02$ , 95% CI [0.01, 0.03];  $P = 1.41 \times 10^{-6}$ ).

The strongest association with BMI among Hispanics was for an interaction between rs10133840 and dietary energy intake ( $\text{Beta}_{\text{interaction}} = -0.01$ , 95% CI [-0.01, -0.005];  $P = 1.28 \times 10^{-6}$ ) (Table 4), a SNP located between the ribosomal protein L15 pseudogene 2 (*RPL15P2*) gene and *LOC730118* on chromosome 14q32.13. Although variation in *CNTNAP2* did not interact with dietary energy intake for BMI, the same SNP that interacted among African-Americans (rs4549702) modified the effect of recreational physical activity on BMI among Hispanics ( $\text{Beta}_{\text{interaction}} = -0.01$ , 95% CI [-0.02, -0.01];  $P = 1.37 \times 10^{-6}$ ).

Among the strongest G×E interactions with BMI in each racial group, we examined effect modification with BMI coded categorically (BMI < 25 [referent] versus BMI = 25.0–29.9, 30.0–34.9, and ≥ 35) and analyzed with logistic regression. Examining the interactions between rs7350721 and years of cigarette smoking among African-Americans and between rs10133840 and dietary energy intake among Hispanics, showed that effect modification was stronger among subjects with higher BMI (> 30) for both interactions (Table 5). The results were not consistent across racial groups.

### WHR Outcome

The strongest G×E interaction for WHR among African-Americans was between SNP rs9557704 in the integrin, beta-like 1 (*ITGBL1*) gene and dietary energy intake ( $\text{Beta}_{\text{interaction}} = -0.04$ , 95% CI [-0.06, -0.03];  $P = 2.17 \times 10^{-7}$ ). Also notable is an association observed between SNP rs11016883 in the methylguanine-DNA methyltransferase (*MGMT*) gene and cigarette smoking (ever/never) ( $\text{Beta}_{\text{interaction}} = 0.01$ , 95% CI [0.007, 0.02];  $P = 8.51 \times 10^{-7}$ ).

The strongest G×E interaction among Hispanics examining WHR as outcome was between the SNP rs5980075, located between *LOC100128521* and motile sperm domain-containing protein 2 isoform 1 (*MOSPD2*) gene, and dietary energy intake ( $\text{Beta}_{\text{interaction}} = 0.04$ , 95% CI [0.03, 0.06];  $P = 5.09 \times 10^{-7}$ ).

## DISCUSSION

Evaluating the WHI GWAS data for G×E interactions affecting both BMI and WHR in two distinct ethnic cohorts of women, we observed several novel interactions. While strong interactions were detected, these interactions did not replicate across cohorts. Possible contributors to the heterogeneity between the two ethnic groups examined include differences in patterns of environmental exposures and demographic histories. Furthermore, since these analyses were conducted using common variants from GWAS, differences in linkage disequilibrium and the potential for latent functional rare variants to be private across racial groups may lead to failure to formally replicate. In this study, all tested environmental/behavioral factors differed between African-Americans and Hispanic subjects. Hispanic subjects had significantly lower BMI and higher WHR than African-Americans. Hispanic subjects were younger, had higher physical activity, dietary energy intake, and alcohol consumption than African-Americans, although they smoked less, and had a smaller proportion of subjects with T2D.

We detected associations between most lifestyle factors and BMI and/or WHR. We observed an inverse association between years of smoking and BMI in African-Americans, and a positive association between both years of smoking and “ever”/“never” smoking and WHR in both ethnicities, which is consistent with previous findings (Chouraki et al., 2008; Simon et al., 1997). There were significant positive associations with BMI and WHR across populations for dietary energy intake and negative associations with BMI and WHR for physical activity and alcohol consumption. Age was negatively associated with BMI but positively associated with WHR in both groups, which is consistent with previous reports that show increasing WHR with age even in the absence of weight gain, and decreasing BMI with age. (Stevens et al., 2010)

The SNP rs10133840 interacted with dietary energy intake in Hispanics and in the meta-analysis. This SNP lies in an intergenic region of chromosome 14q32, bounded by the ribosomal protein L15 pseudogene and dicer 1, ribonuclease type III (*DICER1*) gene. Ribosomal protein L15 pseudogene encodes an untranscribed ribosomal protein; however, *DICER1* is an important mediator of vertebrate development (Murchison and Hannon, 2004) and is essential for life (Bernstein et al., 2003; Wienholds et al., 2003). *DICER1* is a member of the ribonuclease III family and is involved in the processing of microRNAs, which modulate gene expression after transcription (Macrae et al., 2006). Additionally, variation nearby *DICER1* has been associated with the response of blood lipid levels to statin therapy (Barber et al., 2010a). Potential implications for a role of variation in *DICER1* on BMI also include dysregulation of metabolism due to association of *DICER1* variants and risk of multinodular thyroid goiters (Rio et al., 2011). These connections to thyroid dysfunction and lipid homeostasis suggest that this gene plays a role in metabolism and energy balance. Our findings support this model for *DICER1*, and suggest that these effects may also be mediated by dietary energy intake.

SNPs rs141320 and rs2144134, located in the gene serine palmitoyltransferase, long-chain base subunit 3 (*SPTLC3*), interacted with physical activity and alcohol consumption, respectively, with BMI in the meta-analysis. Notably, these interactions were in opposite directions where the interaction with physical activity increased BMI, and the interaction with alcohol decreased BMI. *SPTLC3* encodes an isoform of the third subunit of serine palmitoyltransferase, which catalyzes the rate-limiting step of sphingolipid synthesis. Sphingolipids are important components of cellular plasma membranes, and are involved in cell proliferation, differentiation, senescence, apoptosis, and inflammation, and are particularly enriched in nervous system tissues (Hannun and Obeid, 2002). The sphingolipid synthesis genes are conserved back to yeast and are also essential for embryonic development (Hojjati et al., 2005; Ikushiro et al., 2001; Ikushiro et al., 2003). This gene has also been associated with levels of sphingolipids and bipolar disorder in previous GWAS studies (Alliey-Rodriguez et al., 2011; Hicks et al., 2009).

The SNP rs4549702 in the gene *CNTNAP2* interacted with physical activity to decrease BMI in Hispanics, and interacted with dietary energy intake to increase BMI in African-Americans. *CNTNAP2* is a member of the neurexin superfamily, a group of proteins that mediate cell-cell interactions in the nervous system. Rare recessive genetic variation in *CNTNAP2* has been associated with loss-of-function mutations in epilepsy, intellectual disability, and autism spectrum disorders, accompanied by a range of neuropathologic findings (Strauss et al., 2006). Additional findings suggest associations with specific language impairment, as well as rare mutations in Tourette syndrome, syndromic intellectual disability, and schizophrenia (State MW, 2010). Further support for a connection between *CNTNAP2* and autism was also provided by a whole-exome resequencing study (O’Roak et al., 2011). Previous reports have suggested that autistic patients have increased risk for obesity, even in childhood (Curtin et al., 2010; Tyler et al., 2011), and several mutations

have been observed that seem to confer risk of both obesity and various developmental delays (Bochukova et al., 2010; Dykens et al., 2011; Shinawi et al., 2011; Walters et al., 2010). *CNTNAP2* was also associated with schizophrenia and bipolar in a recent GWAS (Wang et al., 2010), as well as bone mass and geometry (Kiel et al., 2007). The apparent biological relationship between obesity, developmental delay and neurological dysregulation is consistent with a role for *CNTNAP2* in obesity susceptibility, although this association seems to be modified by environmental factors related to energy balance.

The SNP rs1013063 near the gene potassium channel, voltage gated, ISK-related subfamily, member 2 (*KCNE2*) interacted with years of smoking to decrease BMI. *KCNE2* has been associated with lung function (Artigas et al., 2011), height (Lango et al., 2010), and early-onset myocardial infarction (Kathiresan et al., 2009). Studies in humans and mice have also demonstrated that *KCNE2* gene products form a thyroid stimulating hormone-stimulated potassium channel that is required for thyroid hormone biosynthesis (Roepke et al., 2009). *KCNE2* is important for controlling metabolism and energy balance, and smoking or secondary effects on lung function may perturb this regulatory system.

Several other associated SNPs lie nearby or within genes with previously described behavioral, metabolism, or body composition phenotypes. The SNP rs9557704, located in the *ITGBL1* gene interacted with dietary energy intake to increase WHR in African-Americans. Homozygous deletion of the *ITGBL1* gene was observed in a pediatric case with growth hormone deficiency (Cody et al., 2010). The SNP rs7864204, near the gene phosphatidylinositol-4-phosphate 5-kinase, type I, beta (*PIP5K1B*) interacted with recreational physical activity in African-Americans. Variation in *PIP5K1B* has been associated with chronic kidney disease risk in European ancestry individuals (Kottgen et al., 2010). The SNP rs8008758 interacted with alcohol to increase BMI in African-Americans and lies in a paternally imprinted region containing the gene deiodinase, iodothyroline, type III (*DIO3*), which catalyzes the inactivation of thyroid hormone, and has also been associated with type I diabetes risk (Wallace et al., 2010). The SNP rs17002342 in the gene septin 11 (*SEPT11*) interacted with alcohol intake to increase WHR in African-Americans. Variation in *SEPT11* has been associated with schizophrenia and bipolar disorder by a comparative protein expression study in hippocampus samples (Focking et al., 2011). The SNP rs11876941 in the gene deleted in colorectal carcinoma (*DCC*) interacted with history of smoking to increase BMI in the meta-analysis, and *DCC* has been associated with risk of alcoholism (Heath et al., 2011). The SNP rs4877280 near the gene solute carrier family 28, member 3 (*SLC28A3*) interacted with dietary energy intake to increase WHR in the meta-analysis, and has been associated with lipid-lowering response to statins (Barber et al., 2010b). The SNP rs1871045 near the gene poliovirus receptor related 2 (*PVRL2*) interacted with years of smoking in Hispanics to increase WHR. Variation in *PVRL2* has been associated with Alzheimer's disease risk and age of onset in studies of European and African-Americans (Abraham et al., 2008; Kamboh et al., 2011; Logue et al., 2011; Naj et al., 2010), and has also been associated with high-density lipoprotein cholesterol levels in East Asians (Kim et al., 2011). Also the SNP rs10212363 near the gene zona pellucida-like domain containing 1 (*ZPLD1*) interacted with alcohol intake to increase WHR in Hispanics. Variation in *ZPLD1* has been nominally associated with type 2 diabetes in Southeast Asians (Sim et al., 2011).

Although not all interactions had clear relationship with the genes and/or SNPs involved in the interactions based on what is known about these genes and/or SNPs in the literature, agnostic studies like this may provide novel insights into the biology of complex traits. Similarly, some of these models may only seem implausible because little is known about the biology of the implicated genes in the context of lifestyle. We did not obtain conclusive statistical evidence for these models from this study, and so these results will provide



support to future investigations for the candidacy of these genes as obesity risk loci. Many of the SNPs discussed here are plausible candidates for roles in behavior, body size, shape, and composition. Genes implicated in interactions here are involved in metabolic processes, such as endocrine diseases like diabetes, lipid metabolism and transport or bone development and maintenance, or are known neurological factors with effects on development and psychological well-being. While none of the results presented here survive correction for multiple comparisons, they suggest that genes with known effects on metabolism and behavior are likely to modify the roles of important environmental exposures on obesity phenotypes. Accounting for effect modification by behavioral and cultural factors may be essential for discovering the genetic determinants of human obesity, as these phenomena may collectively explain more variance for these traits than direct effects by these genes. These findings merit further replication in necessary in order to validate these interactions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**TABLE 1**

Summary of demographic data

| Variable                                      | African-American (N=8,203) |                 | Hispanic (N=3,484) |                 | P-Value           |
|---|----------------------------|-----------------|--------------------|-----------------|-------------------|
|   | N                          | Mean(S.D)/%     | N                  | Mean(S.D)/%     |                   |
| Age at Interview (years)                      | 8,203                      | 61.6 (7.0)      | 3,484              | 60.3 (6.7)      | <10 <sup>-4</sup> |
| BMI (kg/m <sup>2</sup> )                      | 8,203                      | 31.0 (6.4)      | 3,484              | 28.9 (5.6)      | <10 <sup>-4</sup> |
| <25   | 1,329                      | 16.2%           | 880                | 25.3%           | <10 <sup>-4</sup> |
| 25<-30  | 2,745                      | 33.5%           | 1,355              | 38.9%           |                   |
| 30<-35  | 2,192                      | 26.7%           | 808                | 23.2%           |                   |
| 35  | 1,937                      | 23.6%           | 441                | 12.7%           |                   |
| Waist-Hip Ratio                               | 8,203                      | 0.79 (0.59)     | 3,468              | 0.82 (0.07)     | <10 <sup>-4</sup> |
| Weight (kg)                                   | 8,203                      | 81.9 (17.3)     | 3,484              | 71.6 (14.4)     | <10 <sup>-4</sup> |
| Diabetes                                      | 8,190                      |                 | 3,483              |                 | <10 <sup>-4</sup> |
| No  | 7,047                      | 85.9%           | 3,192              | 91.7%           |                   |
| Yes   | 1,143                      | 13.9%           | 291                | 8.4%            |                   |
| Cigarette Smoking                             | 8,111                      |                 | 3,447              |                 | <10 <sup>-4</sup> |
| Never   | 3,885                      | 47.9%           | 2,150              | 62.4%           |                   |
| Ever  | 4,226                      | 52.1%           | 1,297              | 37.6%           |                   |
| Cigarette Smoking (years)                     | 7,942                      | 1.93 (2.20)     | 3,373              | 1.14 (1.79)     | <10 <sup>-4</sup> |
| Recreational Physical Activity (met-hrs/week) | 8,021                      | 9.7 (12.7)      | 3,312              | 10.8 (13.8)     | 0.0003            |
| Total Dietary Energy Intake (kcal/day)        | 8,190                      | 1,599.6 (950.6) | 3,478              | 1,656.8 (972.2) | 0.001             |
| Alcohol (servings (12 oz. [ounces] /week)     | 8,180                      | 1.10(4.4)       | 3,467              | 1.27(3.8)       | <10 <sup>-4</sup> |
| Alcohol intake                                | 8,190                      |                 | 3,428              |                 | <10 <sup>-4</sup> |
| Non drinker                                   | 1,296                      | 16.0%           | 636                | 18.6%           |                   |
| Past drinker                                  | 2,692                      | 33.3%           | 736                | 21.5%           |                   |
| < 1 drink/month                               | 1,093                      | 13.5%           | 461                | 13.5%           |                   |
| < 1drink/week                                 | 1,535                      | 19.0%           | 778                | 22.7%           |                   |
| 1 to 7 drinks/week                            | 1,130                      | 14.0%           | 643                | 18.8%           |                   |
| 7 drinks/week                                 | 346                        | 4.3%            | 174                | 5.1%            |                   |

TABLE 2

Association between BMI or WHR adjusted for BMI and environmental/behavioral risk factors adjusted for age at interview and ancestry

| Variable                                      | African-American (N=8,203) |               | P                      | Hispanic (N=3,484) |               | P                      |
|---|----------------------------|---------------|------------------------|--------------------|---------------|------------------------|
|   | Beta                       | 95% CI        |                        | Beta               | 95% CI        |                        |
| <b>BMI Outcome</b>                            |                            |               |                        |                    |               |                        |
| Age at Interview (years)                      | -0.09                      | -0.11 - 0.07  | <10 <sup>-10</sup>     | -0.01              | -0.02, -0.005 | 2.31×10 <sup>-4</sup>  |
| Cigarette Smoking (years)                     | -0.10                      | -0.17 - -0.03 | 0.008                  | 0.001              | -0.02, 0.02   | 0.953                  |
| Cigarette Smoking (ever/never)                | -0.09                      | 0.34-0.21     | 0.537                  | 0.05               | -0.04, 0.13   | 0.278                  |
| Recreational Physical Activity (met-hrs/week) | -0.08                      | -0.09 - -0.07 | <10 <sup>-10</sup>     | -0.01              | -0.02, -0.01  | <10 <sup>-10</sup>     |
| Total Dietary Energy Intake (kcal/day)        | 0.03                       | 0.03-0.04     | 1.00×10 <sup>-10</sup> | 0.008              | 0.006, 0.01   | <10 <sup>-10</sup>     |
| Alcohol Intake (categorical)                  | -0.59                      | -0.70 - -0.49 | <10 <sup>-10</sup>     | -0.10              | -0.13, -0.08  | <10 <sup>-10</sup>     |
| <b>WHR Outcome</b>                            |                            |               |                        |                    |               |                        |
| Age at Interview (years)                      | 0.11                       | 0.08-0.14     | <10 <sup>-10</sup>     | 0.15               | 0.11, 0.20    | <10 <sup>-10</sup>     |
| Cigarette Smoking (years)                     | 0.39                       | 0.30-0.48     | <10 <sup>-10</sup>     | 0.36               | 0.19, 0.53    | 3.99×10 <sup>-5</sup>  |
| Cigarette Smoking (ever/never)                | 1.31                       | 0.92-1.70     | <10 <sup>-10</sup>     | 0.96               | 0.34, 1.58    | 0.002                  |
| Recreational Physical Activity (met-hrs/week) | -0.08                      | -0.10 - -0.07 | <10 <sup>-10</sup>     | -0.07              | -0.10, -0.05  | <10 <sup>-10</sup>     |
| Total Dietary Energy Intake (kcal/day)        | 0.03                       | 0.02-0.03     | 1.20×10 <sup>-9</sup>  | 0.02               | 0.005, 0.03   | 0.005                  |
| Alcohol Intake (categorical)                  | -0.39                      | -0.53 - -0.26 | 1.05×10 <sup>-8</sup>  | -0.65              | -0.84, -0.46  | 1.00×10 <sup>-10</sup> |

\* divided variables by 100 to simplify presentation

\* Total dietary energy intake was log transformed

**TABLE 3**

Summary of strongest gene x environment associations with transformed BMI and WHR adjusted for BMI among African-Americans adjusted for age at interview and ancestry.

| <i>Nearby Gene</i>          | Chr. | Interaction                              | Position (bp) | MA | MAF  | Beta <sub>SNP</sub> (95% CI) | Beta <sub>Env</sub> (95% CI) | Beta <sub>Intrxn</sub> (95% CI) | P-Value Intrxn        |
|-----------------------------|------|--|---------------|----|------|------------------------------|------------------------------|---------------------------------|-----------------------|
| <b>BMI Outcome</b>          |      |  |               |    |      |                              |                              |                                 |                       |
| <i>LOC645687//PELL2</i>     | 14   | rs7350721-Smoking(years)                 | 55403266      | C  | 0.09 | -0.01 (-0.02, -0.01)         | -0.15 (-0.22, -0.08)         | 0.41 (0.25, 0.58)               | 5.97×10 <sup>-7</sup> |
| <i>LOC347097//PIP5K1B</i>   | 9    | rs7864204-Recreational Physical Activity | 70418999      | A  | 0.44 | 0.005 (0.002, 0.01)          | -0.04 (-0.06, -0.02)         | -0.04 (-0.06, -0.02)            | 8.70×10 <sup>-7</sup> |
| <i>CNTNAP2</i>              | 7    | rs4549702-Dietary Energy                 | 147531949     | G  | 0.40 | -0.03 (-0.04, -0.01)         | 0.02 (0.01, 0.03)            | 0.02 (0.01, 0.03)               | 1.41×10 <sup>-6</sup> |
| <i>LOC100128373//DIO3OS</i> | 14   | rs8008758-Alcohol Intake                 | 100759798     | A  | 0.25 | -0.01 (-0.02, -0.01)         | -0.70 (-0.83, -0.57)         | 0.39 (0.23, 0.55)               | 2.32×10 <sup>-6</sup> |
| <i>LOC645687//PELL2</i>     | 14   | rs7350721-Smoking(ever/never)            | 55403266      | C  | 0.09 | -0.01 (-0.02, -0.01)         | -0.08 (-0.11, -0.06)         | 0.02 (0.01, 0.02)               | 3.90×10 <sup>-6</sup> |
| <b>WHR Outcome</b>          |      |  |               |    |      |                              |                              |                                 |                       |
| <i>ITGBL1</i>               | 13   | rs9557704-Dietary Energy                 | 101025496     | A  | 0.13 | 0.05 (0.03, 0.07)            | 0.02 (0.02, 0.03)            | -0.04 (-0.06, -0.03)            | 2.15×10 <sup>-7</sup> |
| <i>MGMT</i>                 | 10   | rs11016883-Smoking(ever/never)           | 131390930     | C  | 0.25 | -0.01 (-0.01, -0.003)        | 0.15 (0.12, 0.17)            | 0.01 (0.01, 0.02)               | 8.51×10 <sup>-7</sup> |
| <i>ZNF383D//LOC728516</i>   | 3    | rs1388551-Recreational Physical Activity | 22267575      | A  | 0.17 | 0.01 (0.001, 0.01)           | -0.03 (-0.05, -0.02)         | -0.07 (-0.10, -0.04)            | 1.87×10 <sup>-6</sup> |
| <i>LOC642340</i>            | 2    | rs16827293-Smoking(years)                | 150217578     | A  | 0.12 | 0.01 (0.002, 0.01)           | 0.52 (0.43, 0.62)            | -0.44 (-0.63, -0.25)            | 5.23×10 <sup>-6</sup> |
| <i>SEPT11</i>               | 4    | rs17002342-Alcohol Intake                | 78174229      | T  | 0.13 | -0.02 (-0.03, -0.01)         | -0.30 (-0.45, -0.16)         | 0.61 (0.34, 0.88)               | 9.22×10 <sup>-6</sup> |

\* Beta<sub>SNP</sub>-Beta coefficient for the SNP in the model; Beta<sub>Env</sub>-Beta coefficient for the lifestyle factor included in the interaction; Beta<sub>Intrxn</sub>-Beta coefficient for the interaction term in the model; CI-Confidence interval; Intrxn-interaction

TABLE 4

Summary of strongest gene x environment associations with transformed BMI and WHR adjusted for BMI among Hispanics adjusted for age at interview and ancestry

| Nearby Gene                          | Chr. | Interaction                              | Position (bp) | MA | MAF  | Beta <sub>SNP</sub> (95% CI) | Beta <sub>Env</sub> (95% CI) | Beta <sub>Intrxn</sub> (95% CI) | P-Value Intrxn        |  |
|--------------------------------------|------|--|---------------|----|------|------------------------------|------------------------------|---------------------------------|-----------------------|--|
| <b>BMI Outcome</b>                   |      |  |               |    |      |                              |                              |                                 |                       |  |
| <i>RPL15P2</i>    <i>DICER1</i>      | 14   | rs10133840-Dietary Energy                | 94480282      | C  | 0.14 | 0.01 (0.005, 0.01)           | 0.01 (0.007, 0.01)           | -0.01 (-0.01, -0.005)           | 1.28×10 <sup>-6</sup> |  |
| <i>SLC39A11</i>                      | 17   | rs4969049-Smoking(ever/never)            | 68512535      | C  | 0.17 | -0.001 (-0.002, -0.0004)     | -0.001 (-0.002, 0.0001)      | 0.004 (0.002, 0.01)             | 1.35×10 <sup>-6</sup> |  |
| <i>CNTNAP2</i>                       | 7    | rs4549702-Recreational Physical Activity | 147531949     | G  | 0.34 | 0.001 (0.0003, 0.002)        | -0.01 (-0.01, -0.003)        | -0.01 (-0.02, -0.01)            | 1.37×10 <sup>-6</sup> |  |
| <i>LOC100130240</i>    <i>KCNE2</i>  | 21   | rs1013063-Smoking (years)                | 34620260      | T  | 0.38 | 0.0004 (-0.0003, 0.001)      | 0.07 (0.03, 0.10)            | -0.08 (-0.11, -0.04)            | 4.56×10 <sup>-6</sup> |  |
| <i>LRP8</i>                          | 1    | rs2788032-Alcohol Intake                 | 53550219      | C  | 0.08 | -0.004 (-0.01, -0.002)       | -0.12 (-0.15, -0.09)         | 0.15 (0.09, 0.22)               | 5.68×10 <sup>-6</sup> |  |
| <b>WHR Outcome</b>                   |      |  |               |    |      |                              |                              |                                 |                       |  |
| <i>MOSPD2</i>    <i>LOC100128521</i> | X    | rs5980075-Dietary Energy                 | 14860452      | T  | 0.47 | -0.04 (-0.06, -0.03)         | -0.04 (-0.06, -0.02)         | 0.04 (0.03, 0.06)               | 5.09×10 <sup>-7</sup> |  |
| <i>LOC152225</i>    <i>ZPLD1</i>     | 3    | rs10212363-Alcohol Intake                | 103331251     | A  | 0.22 | -0.02 (-0.03, -0.01)         | -0.64 (-0.86, -0.42)         | 0.73 (0.43, 1.02)               | 1.58×10 <sup>-6</sup> |  |
| <i>CDK4PS</i>    <i>LOC727839</i>    | 1    | rs11184708-Smoking(ever/never)           | 106231810     | T  | 0.13 | -0.01 (-0.02, -0.004)        | 0.002 (-0.004, 0.01)         | 0.03 (0.02, 0.04)               | 2.11×10 <sup>-6</sup> |  |
| <i>BCAM</i>    <i>PVRL2</i>          | 19   | rs1871045-Smoking (years)                | 50018608      | T  | 0.39 | -0.003 (-0.01, 0.002)        | 0.002 (-0.22, 0.23)          | 0.52 (0.30, 0.74)               | 3.95×10 <sup>-6</sup> |  |
| <i>LOC100132060</i>    <i>TBR1</i>   | 2    | rs1064576-Recreational Physical Activity | 161976354     | A  | 0.06 | 0.02 (0.01, 0.03)            | -0.02 (-0.04, -0.001)        | -0.15 (-0.21, -0.08)            | 3.04×10 <sup>-5</sup> |  |

\*Beta<sub>SNP</sub>-Beta coefficient for the SNP in the model; Beta<sub>Env</sub>-Beta coefficient for the lifestyle factor included in the interaction; Beta<sub>Intrxn</sub>-Beta coefficient for the interaction term in the model; CI-Confidence interval; Intrxn-interaction

**TABLE 5**  
 Summary of strongest associated gene x environment associations (TABLE 3 and 4) by BMI strata

| Population               | Interaction                | BMI Category | N     | OR <sub>SNP</sub> (95% CI) | OR <sub>Env</sub> (95% CI) | OR <sub>Intrxn</sub> (95% CI) | P-Value Intrxn        |
|--------------------------|----------------------------|--------------|-------|----------------------------|----------------------------|-------------------------------|-----------------------|
| <b>African-Americans</b> | rs7350721- Smoking(years)  | <25          | 1,329 | 1.00 (Reference)           | 1.00 (Reference)           | 1.00 (Reference)              | -                     |
|                          |                            | 25-<30       | 2,745 | 0.89 (0.73, 1.09)          | 0.97 (0.94, 1.01)          | 1.02 (0.96, 1.10)             | 0.487                 |
|                          |                            | 30-<35       | 2,192 | 0.74 (0.59, 0.92)          | 0.95 (0.92, 0.99)          | 1.12 (1.04, 1.21)             | 0.002                 |
|                          |                            | 35           | 1,937 | 0.65 (0.50, 0.83)          | 0.95 (0.92, 0.99)          | 1.17 (1.07, 1.27)             | 2.03×10 <sup>-4</sup> |
| <b>Hispanics</b>         | rs7350721- Smoking(years)  | <25          | 880   | 1.00 (Reference)           | 1.00 (Reference)           | 1.00 (Reference)              | -                     |
|                          |                            | 25-<30       | 1,355 | 0.96 (0.82, 1.12)          | 1.02 (0.96, 1.09)          | 1.02 (0.95, 1.10)             | 0.502                 |
|                          |                            | 30-<35       | 808   | 1.07 (0.89, 1.28)          | 1.03 (0.96, 1.11)          | 1.02 (0.93, 1.11)             | 0.726                 |
|                          |                            | 35           | 441   | 1.12 (0.91, 1.38)          | 1.01 (0.92, 1.38)          | 0.96 (0.86, 1.07)             | 0.498                 |
| <b>African-Americans</b> | rs10133840- Dietary Energy | <25          | 1,329 | 1.00 (Reference)           | 1.00 (Reference)           | 1.00 (Reference)              | -                     |
|                          |                            | 25-<30       | 2,745 | 2.40 (1.11, 5.20)          | 1.55 (1.11, 5.20)          | 0.48 (0.25, 0.93)             | 0.028                 |
|                          |                            | 30-<35       | 2,192 | 1.23 (0.55, 2.71)          | 2.43 (1.74, 3.37)          | 0.84 (0.43, 1.64)             | 0.607                 |
|                          |                            | 35           | 1,937 | 2.24 (0.92, 5.47)          | 4.76 (3.38, 69.72)         | 0.50 (0.24, 1.05)             | 0.066                 |
| <b>Hispanics</b>         | rs10133840- Dietary Energy | <25          | 880   | 1.00 (Reference)           | 1.00 (Reference)           | 1.00 (Reference)              | -                     |
|                          |                            | 25-<30       | 1,355 | 4.63 (1.90, 11.26)         | 3.93 (2.50, 6.19)          | 0.28 (0.13, 0.61)             | 0.001                 |
|                          |                            | 30-<35       | 808   | 6.36 (2.39, 16.93)         | 7.73 (4.50, 13.26)         | 0.20 (0.09, 0.46)             | 1.74×10 <sup>-4</sup> |
|                          |                            | 35           | 441   | 8.29 (2.25, 30.50)         | 19.94 (10.30, 38.6)        | 0.14 (0.05, 0.44)             | 0.001                 |

\* OR<sub>SNP</sub>-Odds ratio for SNP association in the model; OR<sub>Env</sub>-Odds ratio for lifestyle factor in the model; OR<sub>Intrxn</sub>-Odds ratio for interaction term in the model; CI-Confidence interval; Intrxn-interaction

Summary of strongest gene x environment associations with BMI and WHR adjusted for BMI for random-effects meta-analysis of African-American and Hispanic gene x environment interactions

TABLE 6

| Nearby Gene                 | Chr. | Interaction                              | Position (bp) | MA | Beta(R) | Q    | I <sup>2</sup> | P-Value (R)           |
|-----------------------------|------|--|---------------|----|---------|------|----------------|-----------------------|
| <b>BMI Outcome</b>          |      |  |               |    |         |      |                |                       |
| <i>RPL15P2//DICER1</i>      | 14   | rs10133840-Dietary Energy                | 94480282      | C  | -0.01   | 0.70 | 0.00           | 3.81×10 <sup>-7</sup> |
| <i>SGK1//LOC442261</i>      | 6    | rs1763500-Smoking (years)                | 67343218      | C  | 0.26    | 0.46 | 0.00           | 1.71×10 <sup>-6</sup> |
| <i>PA2G4P2//SPTLC3</i>      | 20   | rs1413020-Recreational Physical Activity | 12678042      | G  | 0.02    | 0.33 | 0.00           | 3.04×10 <sup>-6</sup> |
| <i>SPTLC3//LOC100130692</i> | 20   | rs2144134-Alcohol Intake                 | 13096152      | G  | -0.09   | 0.87 | 0.00           | 3.68×10 <sup>-6</sup> |
| <i>DCC</i>                  | 18   | rs11876941-Smoking (ever/never)          | 49160029      | A  | -0.003  | 0.90 | 0.00           | 4.72×10 <sup>-6</sup> |
| <b>WHR Outcome</b>          |      |  |               |    |         |      |                |                       |
| <i>LOC359819//EEF1B3</i>    | 5    | rs10067755-Smoking (years)               | 134602211     | C  | -0.12   | 0.45 | 0.00           | 1.64×10 <sup>-6</sup> |
| <i>POU3F1//LOC400750</i>    | 1    | rs11802770-Smoking (ever/never)          | 38494250      | T  | 0.01    | 0.57 | 0.00           | 2.90×10 <sup>-6</sup> |
| <i>DNAJC10//FRZB</i>        | 2    | rs10931041-Dietary Energy                | 183393807     | A  | -0.02   | 0.79 | 0.00           | 9.02×10 <sup>-6</sup> |
| <i>SLC28A3//NTRK2</i>       | 9    | rs4877280-Recreational Physical Activity | 86376225      | T  | 0.04    | 0.85 | 0.00           | 8.52×10 <sup>-6</sup> |
| <i>MAML2</i>                | 11   | rs11021499-Alcohol Intake                | 95631777      | A  | -0.39   | 0.48 | 0.00           | 1.86×10 <sup>-6</sup> |