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Genetic and Environmental (Physical Fitness and Sedentary Activity) Interaction Effects on Cardiometabolic Risk Factors in Mexican American Children and Adolescents

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Abstract

Knowledge on genetic and environmental (G × E) interaction effects on cardiometabolic risk factors (CMRFs) in children is limited. The purpose of this study was to examine the impact of G × E interaction effects on CMRFs in Mexican American (MA) children (n = 617, ages 6–17 years). The environments examined were sedentary activity (SA), assessed by recalls from "yesterday" (SAy) and "usually" (SAu) and physical fitness (PF) assessed by Harvard PF scores (HPFS). CMRF data included body mass index (BMI), waist circumference (WC), fat mass (FM), fasting insulin (FI), insulin resistance (HOMA-IR), HDL-cholesterol (HDL-C), triglycerides (TG),

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systolic (SBP) and diastolic (DBP) blood pressure, and metabolic syndrome risk score (MSC). We examined potential G × E interaction in the phenotypic expression of CMRFs using variance component models and likelihood-based statistical inference. Significant G × SA interactions were identified for six CMRFs: BMI, WC, FI, HOMA-IR, MSC, and HDL, and significant G × HPFS interactions were observed for four CMRFs: BMI, WC, FM, and HOMA-IR. However, after correcting for multiple hypothesis testing, only WC × SAy, FM × SAy, and FI × SAu interactions became marginally significant. After correcting for multiple testing, most of CMRFs exhibited significant G × E interactions (Red. G × E model vs. Con. model). These findings provide evidence that genetic factors interact with SA and PF to influence variation in CMRFs, and underscore the need for better understanding of these relationships to develop strategies and interventions to effectively reduce or prevent cardiometabolic risk in children.

Keywords

G × E interaction; genetic variance; genetic correlation; lifestyle modification; physical inactivity; sedentary behavior; childhood obesity

Introduction

Increasing prevalence of cardiometabolic risk factors (CMRFs) such as obesity, and metabolic syndrome (MS) in youth poses an unprecedented public health crisis with profound worldwide impact (Lloyd-Jones et al., 2009). Sedentary behaviors increase the risk of many diseases/disorders such as obesity, type 2 diabetes (T2D), and MS (Knight, 2012). Obesity-related CMRFs now appear in children and adolescents (Fowler et al., 2013; Steinberger et al., 2009), and have been shown to be strong predictors of developing T2D, MS, and CVD in later adulthood (Virdis et al., 2009). Alarmingly, between the years 1980 and 2010, obesity in US children aged 6–11 years has more than doubled, and more than tripled in adolescents aged 12–19 years (Harper, 2006; Ogden, Carroll, Kit, & Flegal, 2012). Since the rising prevalence of CMRFs is a tremendous challenge, there have been attempts to better understand the contributing factors for pediatric CMRFs. Furthermore, the association between sedentary lifestyle and CMRFs in children is controversial because some studies show that a dramatic decrease in physical activity ensues during adolescence (Kimm et al., 2000), and a decrease in physical activity levels appears to be one of the major contributors to the increase in BMI (Brownson, Boehmer, & Luke, 2005).

The rise in obesity among children and adolescents has disproportionately affected Mexican American (MA) children. Recently, our data on CMRFs in MA children aged 6–17 years in San Antonio, Texas revealed a high risk of overweight (53%), obesity (34%), MS (19%), and pre-diabetes (13%) (Fowler et al., 2013). These data stand in stark contrast to comparable National Health and Nutrition Examination Survey (NHANES) 2009–2010 data on U.S. children and adolescents (ages 2–19 years) where the prevalence of obesity was estimated to be 16.9% (Males 17.8% and Females 15.9%) with significant ethnic disparities in obesity prevalence: European Americans = 14.0%, African Americans =24.3%, and MAs = 21.2% (Ogden et al., 2012). Pediatric obesity and insulin resistance are the key factors among the CMRFs and are predictors of adult obesity, T2D, MS and CVD (Lloyd-Jones et

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al., 2009; Virdis et al., 2009). Particularly, abdominal fat is an important risk factor underlying the many facets of the MS and related factors, such as glucose intolerance, hyperinsulinemia, and hypertriglyceridemia (Despres et al., 2008).

CMRFs are influenced by both genetic and environmental factors (i.e., dietary intake and physical activity), and their interactions (Andreasen & Andersen, 2009; Arya et al., 2015; Jermendy et al., 2011; Santos et al., 2013). Environmental factors such as lifestyle and healthy/unhealthy behaviors and obesogenic environments (e.g., fast food restaurants, sitting or lying down and watching TV, and TV viewing time) (Bai et al., 2016; Santos et al., 2014) substantially influence variation in CMRFs. Thus, physical activity, physical fitness, and sedentary behavior are thought to be important determinants of CVD, T2D, hypertension, and MS (Blair & Haskell, 2006; DeFina et al., 2015; Hamilton, Hamilton, & Zderic, 2007; Lloyd-Jones et al., 2009; Ortega, Ruiz, Castillo, & Sjostrom, 2008). Most importantly, as (Ortega et al., 2008) stated, their role is critical during the developmental stages of childhood and adolescence since lifestyle and healthy/unhealthy behaviors are established during these early years with potential impact on behavior and health status later in life.

Sedentary lifestyle has been identified as a major risk factor for several of CMRFs including obesity, insulin resistance and heart disease. Several epidemiological and intervention studies have identified the role of sedentary activity and physical fitness for overweight and obesity in children and adolescents (Butte, Cai, Cole, & Comuzzie, 2006; Butte, Puyau, Adolph, Vohra, & Zakeri, 2007; Chung, LPY, ECK, & JWY, 2014; Esmaeilzadeh & Ebadollahzadeh, 2012; Ortega et al., 2008). On the other side of the equation, genetic factors explain 20–86% of variation in body weight, BMI, and fat mass (Choquet & Meyre, 2011; Fowler et al., 2013; Lloyd-Jones et al., 2009; Sonestedt et al., 2009). However, there is a paucity of data on how gene by environment (G × E) interaction influences CMRFs, especially in children and adolescents (Fisher, Smith, van Jaarsveld, Sawyer, & Wardle, 2015; Graff et al., 2011; T. Huang & Hu, 2015). Therefore, the purpose of this study was to examine G × E (i.e., G × PF and G × SA) interaction effects on CMRFs in MA children and adolescents (N=617), who participated in our San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study. Given that this study utilizes the family-based data, it has well-known advantages to assess the extent to which the clustering of CMRFs is influenced by common genetic factors and their interactions with shared common environments (Vincent P. Diego, Kent Jr, & Blangero, 2015; J. L. Hopper, 1993; J. L. Hopper, Visscher, P.M., 2005).

Subjects and Methods

The Study Subjects: San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study

We conducted a genetic epidemiologic study of MS, and its related cardio-metabolic risk factors (CMRFs) in Mexican American Children, called the San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study, involving 673 MA children (ages 6–17 years; 401 nuclear families; 3,664 relative pairs [e.g., sibling pairs = 383, and first-cousin pairs = 550]), which was described in detail previously (Fowler et al., 2013). SAFARI children were the offspring of predominantly low-income extended families previously

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enrolled in one of three community-based genetic epidemiologic studies of MA adults in San Antonio, Texas, as detailed in (Fowler et al., 2013). As part of the SAFARI study, we collected demographic, phenotypic, and environmental data including nutrition and physical activity information from SAFARI children using standard procedures. However, for this study, we only considered 617 SAFARI children for whom environmental (i.e., physical fitness and sedentary activity) data were available.

Phenotype Data

Family history, demographic, phenotypic, and environmental data were obtained for SAFARI participants as reported earlier by (Fowler et al., 2013). Blood samples were obtained after a 10-h overnight fast and used to measure metabolic parameters including fasting plasma glucose and insulin, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) following standard protocols. Anthropometric measurements such as height, weight, body mass index (BMI), waist circumference (WC), and blood pressure (systolic (SBP) and diastolic blood pressure (DBP) were collected using standardized protocols, as described previously (Fowler et al., 2013). Fat mass (FM) was measured using dual-energy-X-ray absorptiometry (DXA Hologic). Using FPG and FI values, homeostasis model of assessment - insulin resistance (HOMA-IR) was derived using the University of Oxford Diabetes Trials Unit HOMA2-IR calculator (http://www.dtu.ox.ac.uk/homacalculator) (Matthews et al., 1985). The number of MS components (MSC) that we previously assessed was used as a semi-quantitative trait (range: 0–5 in our data), and the MS components include abdominal adiposity, hyperinsulinemia, glucose intolerance, hypertriglyceridemia, low HDL-C, and elevated SBP and/or DBP (Fowler et al., 2013).

Assessment of Sedentary Activity (SA)

Sedentary activities (SAs) were measured using the Girls Health Enrichment Multi-Site Studies (GEMS) Activity Questionnaire (GAQ) developed by Treuth et al. (Treuth et al., 2004). Sedentary activities performed yesterday (SAy) and usually (SAu), both having five categories of estimated time spent (none, <30 min, 30 min to 1hr, 1–3 hrs, >3 hrs), were recorded; and codes were assigned for each of the time categories as follows: none = 0; <30 min = 0.25, 30 min–1hr = 0.75, 1–3 hrs = 1.5, and >3 hrs = 2.5. The GAQ summary scores for sedentary activity (SAy and SAu) were computed as the sum of weights for all sedentary activities divided by the number of non-missing items. The numeric values assigned to answers were arbitrarily selected a priori, based on judgment to reflect monotonically increasing values (Treuth et al., 2004). Simulation studies have shown that ordinal variables with 5 categories can be safely regarded as continuous in that the type I error rate for hypothesis testing involving such traits is well controlled, power is sufficient (≥ 0.80), and associated parameter estimates are unbiased and efficient (Rhemtulla, Brosseau-Liard, & Savalei, 2012; Savalei & Rhemtulla, 2013). Thus, SAy and SAu were both treated as continuous variables in our analyses.

Assessment of Physical Fitness

We used a modified Harvard Step Test (Trevino et al., 2004) to assess physical fitness (PF). A child was asked to step up and down (both feet) from a stool (30 cm high) at the rate of thirty cycles per minute for 5 minutes or until exhaustion. Heart rates were recorded at 0, 1,

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and 2 minutes post exercise. The Harvard physical fitness Score (HPFS) was calculated as: total duration of exercise in seconds × 100, divided by the sum of three post-exercise heart rates.

SNP Selection and Genotyping

We selected 96 previously identified GWAS/literature reported risk SNPs for cardio-metabolic traits (Kathiresan et al., 2008; Kooner et al., 2011; Willer et al., 2008)(http://www.genome.gov/gwastudies) as described in detail in our ongoing unpublished work (Farook et al.) for this study. Genomic DNA was extracted from blood samples collected from the MA children who participated in the SAFARI study, using Qiagens's QIAmp DNA 96 BLOOD KIT or QIAmp DNA BLOOD MINIKIT according to the manufacturer's protocol. Genotyping of the 96 SNPs was done using the Illumina's Goldengate Veracode Assay per the manufacturer's protocol (Illumina, San Diego, CA; www.illumina.org).

Statistical Analysis

We used the program SOLAR (http://www.txbiomedgenetics.org/solar) to perform genetic analyses including estimation of heritabilities (h^2) and G × E interaction modeling using variance components approaches (Almasy & Blangero, 1998). Each phenotype was first regressed against age, age^2, sex, age-by-sex, age^2-by-sex and pubertal status, and then the regression residuals thus derived for each trait were normalized using an inverse normal transformation as previously described (Blangero et al., 2013; V.P. Diego et al., 2007).

Genotype-by-Environment (G × E) Interaction Model for Continuous Environments

We examined G × E interaction effects in response to the SA and PF environments by modeling the additive genetic variance and correlation as continuous functions of the environment. We describe our methods in terms of SA for convenience but they apply to PF as well. Regarding G × SA interaction, the fundamental null hypothesis is that the expression of a polygenotype (i.e., aggregate of all genotypes related to the expression of a phenotype) is independent of SA levels. For the simplest case of a trait analyzed under two environments, the G × E interaction variance is zero if the following two conditions are simultaneously true: 1) Homogeneity in the additive genetic variance: $\sigma^2_{g1} = \sigma^2_{g2} = \sigma^2_g$, where σ^2_{g1} and σ^2_{g2} are the additive genetic variance in environments 1 and 2, respectively; 2) The genetic correlation (ρ_g) is one across environments: $\rho_g = 1$. Rejection of either hypothesis rejects the overall null hypothesis of no G × E, and is taken as evidence of G × E interaction. (Blangero, 2009; V.P. Diego, Almasy, Dyer, Soler, & Blangero, 2003). Thus, there is no G × SA interaction, for a given CMRF, if it is simultaneously true that the genetic correlation for the trait is equal to 1.0 across different levels of SA and the trait additive genetic variance is homogeneous across all levels of SA.

We modeled the variance and correlation as functions of SA levels. For the genetic variance function (and similarly for the environmental variance), we modeled the variance using an exponential function of SA levels, where the exponential function maintains positivity, which is required of a variance (Blangero, 2009; V.P. Diego et al., 2003): $\sigma^2_g = \exp[\alpha_g + \gamma_g(SA)]$, where α_g and γ_g are parameters to be estimated. On taking the natural logarithm of the exponential function the variance homogeneity null hypothesis holds for a slope-term

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equal to 0: $\gamma_g = 0$. The genetic correlation was modeled using the exponential decay function of the pair-wise differences in SA levels: $\rho_g = \exp[-\lambda|SA_x - SA_z|]$ where SA_x and SA_z are the values of the SA for any two individuals x and z. The null hypothesis that the genetic correlation is equal to 1 is equivalent to $\lambda = 0$ because in this event: $\rho_g = \exp[-\lambda|SA_x - SA_z|] = e^0 = 1$.

We carried out model evaluations and hypothesis testing in two stages as follows. In the first stage, we examined whether the overall G × E interaction model provided a better fit to the data when compared with the polygenic model by way of a likelihood ratio test (LRT). It can be shown that the polygenic model is nested within the full G × E interaction model and that relative to the polygenic model the G × E interaction model has three additional parameters (the three being γ_g, γ_e, and λ; α_g and α_e are reparameterized versions of the variances). The LRT statistic for this comparison is distributed as a 50:50 mixture of chi-squares with 2 and 3 df (V.P. Diego et al., 2003). In addition, we also critically evaluated the full G × E interaction model by examining the parameter values relative to their standard errors for the gamma and lambda parameters.

In the second stage, if the full G × E interaction model was found to better fit the data than the polygenic model and if the parameter MLEs were at least larger than their standard errors, then we examined the more specific G × E interaction hypotheses. Here, the full G × E model with all parameters estimated was compared with models where either gamma (γ) or lambda (λ) were constrained to 0 to respectively test the hypotheses of additive genetic variance homogeneity and a genetic correlation equal to one. The distributions of the LRT statistics are respectively a chi-square with 1 df, and a 50:50 mixture of a chi-square with a point mass at 0 and a chi-square with 1 df (V.P. Diego et al., 2003).

If parameters were judged to be unimportant (i.e. where the standard error is greater than the maximum likelihood estimate), we constrained such parameters to 0 and tested the remaining potentially important parameter(s) under a reduced version of the G × E interaction model. In most cases of the reduced G × E interaction model, we constrained two of the three additional parameters in the full G × E interaction model (the three being γ_g, γ_e, and λ) leaving one free parameter for inferring G × E interaction. The distributions of the LRTs in these cases where gamma (γ) or lambda (λ) were constrained to 0 as appropriate are respectively a chi-square with 1 df, and a 50:50 mixture of a chi-square with a point mass at 0 and a chi-square with 1 df. Power to detect an interaction effect was computed using standard methods (Blangero et al., 2013; V. P. Diego, Kent, J.W., Blangero J., 2015).

G × E Analysis with SNPs

Prior to G × E analysis with SNPs, we performed association analysis between the SNPs and three environmental variables (HPFS, SAy, and SAu) using the measured genotype approach (MGA) to select the SNPs that are associated ($p < 0.05$) with the environments, which were selected based on our ongoing work by our group (Farook et al.,. unpublished). We then selected the top three SNPs (one per environment) and performed the G × E interaction analysis while simultaneously modeling SNP effects.

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Where necessary, multiple-hypothesis testing correction was carried out by controlling the false discovery rate at the 0.05 level (39). Further, we performed FDR control according to the hypothesis examined. Thus, FDR control was carried out for each of the two mechanisms for G × E interaction, and for the genetic association tests.

Results

The characteristics of the study subjects are presented in Table 1. The mean age of subjects was 11.7 years and 48.8% were girls. The prevalence of pre-diabetes (Impaired Fasting Glucose [IFG], Impaired Glucose Tolerance [IGT] or both), overweight, obesity, and metabolic syndrome were 13.3%, 53.8%, 33.7%, and 18.6%, respectively. The CMRF trait sample sizes varied from 599 (HOMA-IR) to 617 (MSC) reflecting missingness patterns and exclusion of trait specific outliers (i.e., values ± 4 SD from the mean were excluded from genetic analysis). The sample sizes available for environmental variables ranged from 474 (Harvard fitness scores) to 617 (sedentary activity_yesterday). Means and SDs were presented for all CMRFs and environmental variables. We found strong genetic influences for all the CMRFs. As reported in Table 1, heritabilities (h^2) ranging from 0.43 [FG, $p = 5.2 \times 10^{-5}$] to 0.79 [BMI, $p = 5.1 \times 10^{-11}$] for a majority of CMRFs were strong to moderate in magnitude, and highly significant (<0.001).

G × E Interaction Findings

The polygenic model was compared to the G × E interaction model by means of a log-likelihood ratio test (see table 2). The G × E (PF/SA) interaction model is significantly better than the polygenic model for BMI (G × SAy), FM (G × HPFS and G × SAy), FI (G × PF and G × SAy), and DBP (G × SAu), and marginally non-significant for BMI (G × PF), HIR (G × ±PF, G × SAu, and G × SAy), MSC (G × SAy), and HDL (G × SAy). For all 6 marginally non-significant test results, we found that the neither of the gamma parameters for additive genetic or environmental variance heterogeneity were important (data not shown). We therefore constrained the gamma parameters to 0 and analyzed a reduced G × E interaction model in which the alpha parameters for the additive genetic and environmental variances and the lambda parameter for the genetic correlation are free to be estimated.

Although the polygenic model considerably outperformed the full G × E interaction model for WC for all three environments, we decided to move forward with these trait-environment constructs because two of the three “additional” parameters had larger standard errors relative to their MLEs. For the WC × PF and WC × SAu analyses we found that only the genetic correlation parameter had the possibility of being important whereas for the WC × SAy analysis we found that only the additive genetic variance heterogeneity parameter had the potential to be important under a reduced interaction model. The above 9 situations had in common the characteristic that the full G × E interaction model perhaps did not perform well relative to the polygenic model due to being overburdened with unnecessary parameters. For the FI × SAu, FI × SAy, and DBP × SAu interaction models, however, we found that although their full G × E interaction models performed significantly better than the polygenic model at explaining the data, the significant result seemed to arise from only important parameter (the gamma parameter for the additive genetic variance for the former

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two and the lambda parameter for the lattermost). Thus, for these three models, we moved forward with their appropriately reduced versions of the G × E interaction model.

We then tested the specific G × E interaction null hypotheses under either the full or reduced G × E interaction model as appropriate. As shown in Table 3, BMI, WC, FM, FI, HOMA-IR, MSC, HDL, and DBP exhibited significant G × E interaction (Red. G × E model vs Con. model) after correcting for multiple testing. Specifically, significant G × HPFs interactions were detected for BMI, FM, and HOMA-IR, while G × SAy interactions were detected for BMI, FI, HOMA-IR, and HDL, and G × SAu interactions were detected for WC, MSC, HDL and DBP. Among the significant interactions, multiple testing correction was not needed for BMI_SAy, FM_HPFs, MSC_SAu, HDL_SAy, and DBP_SAu as indicated in Table 3. However, WC-SAy, FM-SAy, and FM-SAu were not significant.

As shown in Table 3 and Figure 1, for BMI_SAy, FM_HPFs, FI_SAy and DBP_SAu, the null hypothesis of genetic variance (σ^2_g) homogeneity was rejected. The null hypothesis of homogeneity in the genetic variance implies a straight line graph (i.e. slope equal to 0) at the level of the natural logarithm of the heritability given that the variances are modeled as exponential functions. Thus, Figure 1 shows that the genetic variance changes as a function of the physical activity environment. In particular, the genetic variance increases with increasing HPFS for fat mass (Figure 1, left panel), and with increasing sedentary activity (yesterday or usual) or DBP, FI, BMI, and WC (Figure 1, right panel). For perspective, we plotted the expected variance lines under the null hypothesis of variance homogeneity for fat mass at the left panel and for DBP at the right panel. Taken together, these curves illustrate heterogeneity in the additive genetic variance as a function of some environmental exposure (HPFS for the left panel and sedentary activity for the right panel).

As shown in Table 3 and Figure 2, for BMI_HPFS, BMI_SAy, WC_HPFs, WC_SAu, FM_SAy, HOMA-IR_SAu/SAy/HPFS, MSC_SAu, and HDL_SAy, the null hypothesis of a genetic correlation equal to 1 was rejected. The null hypothesis of a genetic correlation equal to 1 as a function of pairwise differences in the environmental exposure is illustrated by the horizontal dotted line at a value of 1 for the genetic correlation. When this hypothesis is rejected, the lambda parameter is significant and we then observe genetic correlation functions that decay away from 1 with increasing differences in environmental exposure. In Figure 2, G × SAy interactions, both significant (BMI) and suggestive (HOMA-IR) were observed (solid lines). Due to the small sample size of our study, most trait-environment test cases in Table 3 were underpowered for G × E detection with only BMI_SAy (for the genetic variance and correlation) and FM_HPFS having power greater than 0.8 for G × E detection. Suggestive G × SAu interaction was observed for WC, HOMA-IR and MSC (dotted lines). Similarly, G × PF (i.e., Harvard fitness score) interactions, both significant (BMI) and suggestive (WC), due to the genetic correlation were observed (Figure 2). It can be seen that the genetic correlation decreases as the pair-wise differences for an environmental measure increases. BMI was the only trait for which the null hypotheses for the genetic correlation and the genetic variance were rejected, in relation to SAy. Figure 3 depicts the variance and correlation functions for BMI simultaneously as a covariance function, demonstrating that G × SAy interaction for BMI is a joint function of genetic variance heterogeneity and a genetic correlation different than one.

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As reported in Table 4, our G × E models were successful in detecting genetic association with the 3 SNPs in 34 out of 45 trait-environment test scenarios (10 for G × HPFS, 11 for G × SAu, and 13 for G × SAy) after multiple testing correction (FDR = 0.05).

As shown in Table 4, we used our G × E models to study any potential genetic association with three SNPs that showed nominal associations ($p < 0.05$) with three environments: rs1333049 to be associated with HPFS, rs1698692 to be associated with SAu, and rs12695382 to be associated with SAy. We refer to this model as a measured genotype (mg)-G × E model because it jointly accounts for a measured genotype effect at a SNP while simultaneously accounting for potentially important G × E interaction effects.

As can be seen in Table 4, the mg-G × E model is quite successful at establishing proof of principle that we are able to simultaneously account for a measured genotype effect at a SNP and for a G × E interaction effect. Out of 45 test cases, 34 were significant after multiple testing correction (FDR = 0.05). All the three SNPs that were included in our G × E models found to be associated with cardio-metabolic traits in our data. e.g. rs1333049 (*LOC729983*) with triglycerides (TG) [$P = 3.9 \times 10^{-3}$], MS [$P = 0.01$], MSC-N [$P = 9.2 \times 10^{-3}$]; rs16986921 (*CTNNBL1*) with DBP ($p = 0.03$); rs12695382 (*B4GALT4*) with Fasting Insulin (FI, $p = 0.03$), and HOMA-IR [$p = 0.03$].

Discussion

We investigated the impact of G × E interaction on CMRF variation in MA children, who were previously found to be at higher risk for childhood obesity and its clinical correlates (Fowler et al., 2013). We determined moderate to high heritabilities for key CMRFs prior to performing G × E interaction analyses. It is important to note that sedentary behavior measures were not correlated with the physical fitness measure in our study, which is consistent with a previous report (Kerner, Kurrant, & Kalinski, 2004). Also, as reported earlier, the correlation between obesity measures and PF was negative, whereas it was positive with SA measures (Must & Tybor, 2005). Significant G × E (SA or PF] interactions were detected for the following CMRFs: BMI, FM, WC (obesity/abdominal obesity), HOMA-IR (insulin resistance), and MSC. The inference of G × E (SA or PF] interactions was drawn from observations of heteroscedasticity in the additive genetic

As shown in Figure 1, the genetic variance increases with increasing SA or PF. Likewise, as can be seen from Figure 3, the proportion of phenotypic variance in BMI that is attributable to additive genetic variance is larger in children with low sedentary activity compared to children with high levels of sedentary behavior. These findings suggest that there may be different genetic mechanisms underlying the physiology of sedentary behavior versus physical fitness. This observation warrants further studies to differentiate between the unique molecular and physiologic effects underlying sedentary behavior compared with physical fitness (Hamilton et al., 2007).

It is evident from these analyses that the phenotypic expression of a given trait may be influenced by the interactions between genotype (i.e., polygenotype) and environmental exposure. Thus, if a child is already at significantly increased risk for a given health

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condition due to genetic susceptibility, the environmental exposures assessed in this study (SA or PF) appear to significantly alter or modulate the child's already heightened metabolic risk. Taken together, the interaction findings of this study specifically correspond to the interrelated metabolic conditions of obesity/abdominal obesity and insulin resistance with direct relevance to prediabetes, T2D, and MS. Our interaction observations can be interpreted to support the possibility that physical inactivity/sedentary lifestyle may either up-regulate genes with normal homeostatic functions for both weight maintenance and insulin sensitivity, or increase expression of susceptibility genes for obesity and insulin resistance – or do both simultaneously, across different sets of genes (Bey et al., 2003; Hamilton et al., 2007). For example, it was found that inactivity upregulated the expression of a number of genes in skeletal muscle in a rat model (Bey et al., 2003; Hamilton et al., 2007). Hojbjerre et al. (Hojbjerre et al., 2011) reported in human subjects before and after bed rest that physical inactivity was associated with higher levels of tumor necrosis factor α, a potent mediator of inflammation-related gene expression (Hotamisligil, 2006).

Sedentary activity has been associated with increased risk of obesity, T2D, CVD, and premature mortality. Bai and colleagues (Bai et al., 2016) demonstrated that screen time is a stronger predictor of weight status than physical activity in children and adolescents, and that physical activity is strongly correlated with cardiorespiratory fitness only in adolescents. Graf et al. (Graff et al., 2011) found significant interactions between screen time and genetic factors during adolescence that influence body mass changes between adolescence and young adulthood. Consistent with these studies, our findings revealed remarkable G × SA interaction influences on CMRFs (i.e., BMI, WC, HOMA-IR, and MSC) in MA children.

A number of studies have highlighted the detrimental effects of physical inactivity and the burden of inactivity-induced chronic diseases (Katzmarzyk, 2010; Tremblay, Colley, Saunders, Healy, & Owen, 2010). While exercise or physical activity is prescribed as the best treatment and/or prevention option for many chronic metabolic diseases, one of the contributing factors to the development of many metabolic diseases is considered to be the sedentary activity or physical inactivity. For example, cessation of exercise led to significant accumulation of intra-abdominal fat within 21 days in an animal model (Laye, Thyfault, Stump, & Booth, 2007). Slentz et al. (Slentz, Houmard, & Kraus, 2009) examined the effects of exercise on CMRFs. They found that there were cumulative detrimental effects in the inactive control group over only six months, and observed significant increase in weight and visceral fat. Within another six months of sedentary activity, they also noticed further deterioration in health.

The deleterious effects of abdominal obesity and its consistent association with other key CMRFs such as T2D, MS, and CVD in children and adolescents have been highlighted in several studies (Despres et al., 2008; Fowler et al., 2013). Sedentary activity is positively associated with abdominal obesity, while physical activity shows inverse association (Butte et al., 2007; Y. Kim & Lee, 2009). Studies based on directly measured PA suggest that high levels of PA or increased time spent in vigorous PA are associated with lower abdominal obesity (Y. Kim & Lee, 2009; Saelens, Seeley, van Schaick, Donnelly, & O'Brien, 2007). Thus physical inactivity or sedentary activity is considered to be an important causal factor of abdominal obesity. Given these complex relationships between abdominal obesity and

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physical in activity/sedentary behavior, it is noteworthy that our study revealed that waist circumference, a surrogate measure of abdominal obesity, is not only under substantial additive genetic influences, but also is influenced by G × SA or PF interaction effects in MA children.

With recent advances in susceptibility gene discoveries using genome-wide association scans, there has been an increased interest in identifying genes that may influence susceptibility to adiposity and its clinical correlates through gene-environmental interactions (Andreasen & Andersen, 2009; Bai et al., 2016; T. Huang & Hu, 2015; Jermendy et al., 2011; J. Y. Kim et al., 2016; Marti, Martinez-Gonzalez, & Martinez, 2008). There is strong evidence that genetic susceptibility to obesity can be altered through physical activity (Choquet & Meyre, 2011; Marti et al., 2008). It was shown that carriers of the Trp64Arg mutation in the *ADRB3* gene with low levels of recreational physical activity have a higher risk of developing obesity (Marti et al., 2008). Several studies showed a strong interaction between the *FTO* genotype and physical activity on obesity risk in adults and adolescents (Andreasen & Andersen, 2009; Andreasen et al., 2008; Sonestedt et al., 2009). Li et al. (Li et al., 2010) used a genetic predisposition score based on the information from 12 obesity associated SNPs and found that high level of physical activity accounted for 40% reduction in the genetic predisposition to common obesity. In another study, Ochoa et al. (Ochoa, Moreno-Aliaga, Martinez-Gonzalez, Martinez, & Marti, 2006) assessed the relationship between the *ADRB2* Gln27Glu polymorphism and TV viewing in Spanish children and adolescents and found interaction between this polymorphism and the number of hours spent watching TV with a significant effect on obesity risk (Ochoa et al., 2006). In European populations, gene-environment studies have reported that the association between the *FTO* gene and BMI is attenuated by physical activity levels (Andreasen et al., 2008; Rampersaud et al., 2008; Vimaleswaran et al., 2009). In the Old Order Amish population, physical activity was found to be inversely associated with lower BMI (Rampersaud et al., 2008). Although such association was only observed in individuals homozygous for a FTO risk allele, it was not observed in individuals with the protective allele (Rampersaud et al., 2008). Thus gene-environment studies indicate an association between variance due to specific genotypes and lifestyle as demonstrated by the *FTO* gene and physical activity.

Our findings from an exploratory G × E interaction analysis with SNPs further demonstrate their potential contribution to the observed interaction effects in CMRFs. Interestingly, all the 3 SNPs examined in our study were associated with several CMRFs. For example, rs1333049 is associated with coronary artery disease (Samani et al., 2007); rs16986921 is associated with BMI and fat mass (Liu et al., 2008); and rs12695382 is associated with LDL (Willer et al., 2008). Several of these SNP associations in our study had the same direction of effect reported previously in the European GWAS and the same risk alleles. For example, these included the risk alleles for: rs1333049 (C; MAF = 0.48, reported 0.47 – 0.49). These results are in agreement with our earlier findings. As a group, we have previously demonstrated that G × E modeling can increase power to detect quantitative trait loci (QTLs) using short tandem repeat marker data (V.P. Diego et al., 2003; Puppala et al., 2007; Voruganti et al., 2011) and expression QTLs using gene expression data (Kent et al., 2012).

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In addition to environmental stimuli, sedentary behavior can be caused by neurological disorders and their underlying genetic factors. Given that there is a neurobehavioral basis for increased sedentary behavior or low physical activity, it follows that sedentary behavior may in fact be substantially underlain by genetic factors. Indeed, a number of neurological and psychiatric disorders, known to have a strong genetic component, manifest lethargy, or deficits in motor functioning. Such disorders include depression (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005), cerebral palsy (Peterson, Gordon, & Hurvitz, 2013), movement disorders (Y. Huang, Yu, Wu, & Tang, 2014), and Parkinson Disease and Multiple Sclerosis (Ellis & Motl, 2013). Thus, it is quite possible that our observed gene-sedentary behavior interactions may be mediated by the genetic effects underlying sedentary behavior (which imply a kind of gene-gene interaction) as opposed to its truly environmental component. Future investigations are very much needed to pursue or develop approaches to clearly delineate the genetic and environmental components of sedentary behavior, and its role in the phenotypic determination of cardiometabolic risk factors. We plan to explore this issue in our future studies.

Our study has some limitations that warrant discussion. First, the sample size of our family-based data was modest. Second, assessment of sedentary activity through a self-administered questionnaire is sometimes poor in children due to cognitive ability. Third, common household effects were not accounted for in the estimation of heritabilities, which may be slightly inflated. Lastly, the environments used in the study are shown to have a genetic component; therefore, there is a possibility for our interaction models to reflect gene × gene interaction.

Conclusions

We found strong and highly significant genetic influences for all the examined CMRFs in this study involving Mexican American children and adolescents who participated in our SAFARI study. We observed significant G × SA and G × PF interaction effects on CMRFs, specifically in measures of obesity/abdominal obesity and insulin resistance. We also identified the measured genotype effects of specific genetic variants and G × E interaction effects simultaneously that influence susceptibility to cardiometabolic risk factors. These findings provide evidence that sedentary lifestyle and physical fitness patterns interact with additive genetic factors to influence the phenotypic expression of CMRFs, perhaps with distinct molecular and physiological repertoires. The ability to identify children with elevated susceptibility to obesity-related traits would be critical to initiating effective early prevention strategies or to treat children in these at-risk groups.

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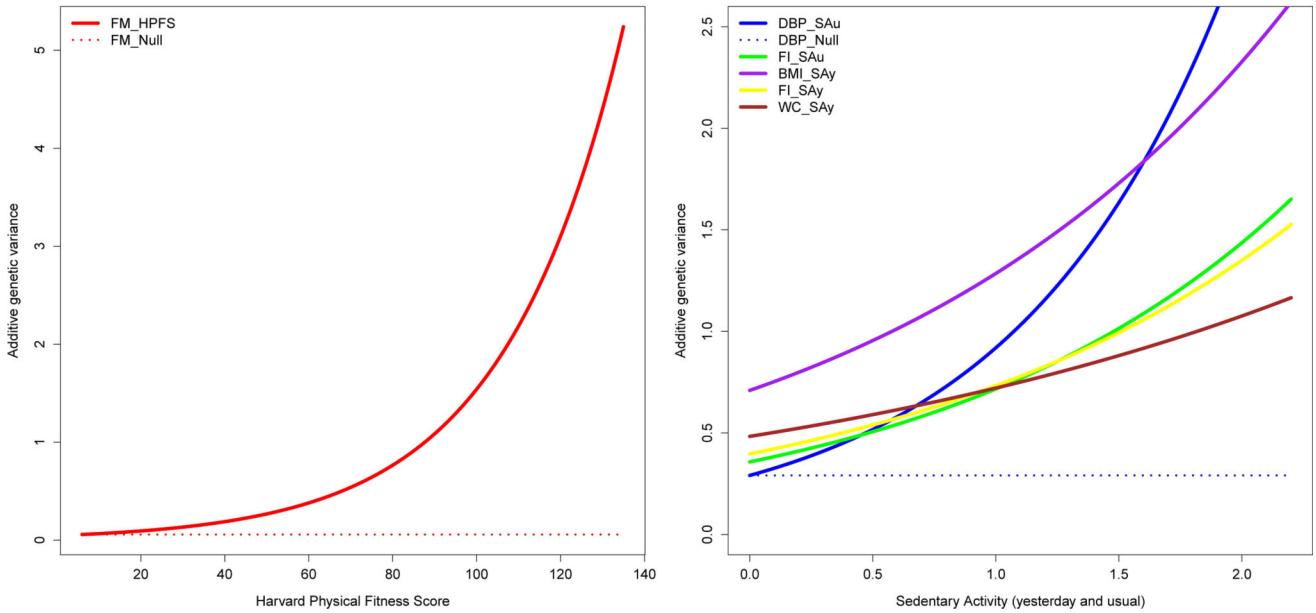

Figure 1.

Additive Genetic Variance Functions. Left panel: Fat Mass_HPFS. Right panel: DBP_SAu (blue), FI_SAu (green), BMI_SAy (purple), FI_SAy (yellow), and WC_SAy (brown).

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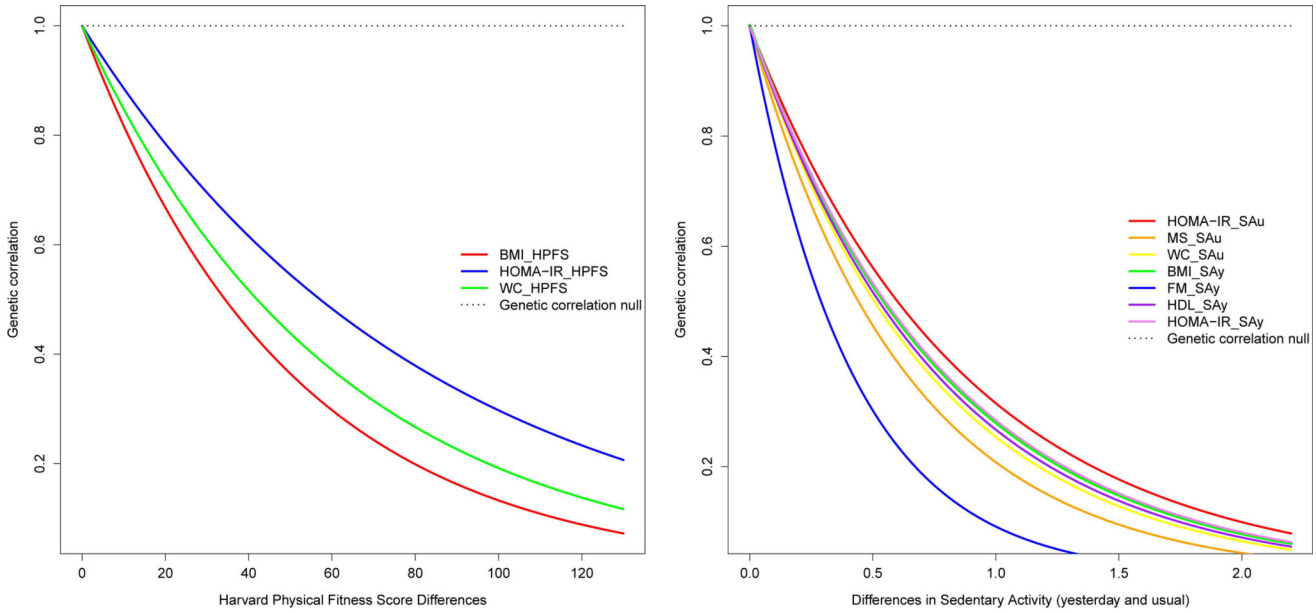

Figure 2.

Genetic Correlation Functions. Left panel: BMI_HPFS (red), HOMA-IR_HPFS (blue), and WC_HPFS (green). Right panel: HOMA_IR_SAu (red), MSC_SAu (orange), WC_SAu (yellow), BMI_SAy (green), FM_SAy (blue), HDL_SAy (purple), and HOMA-IR_SAy (violet).

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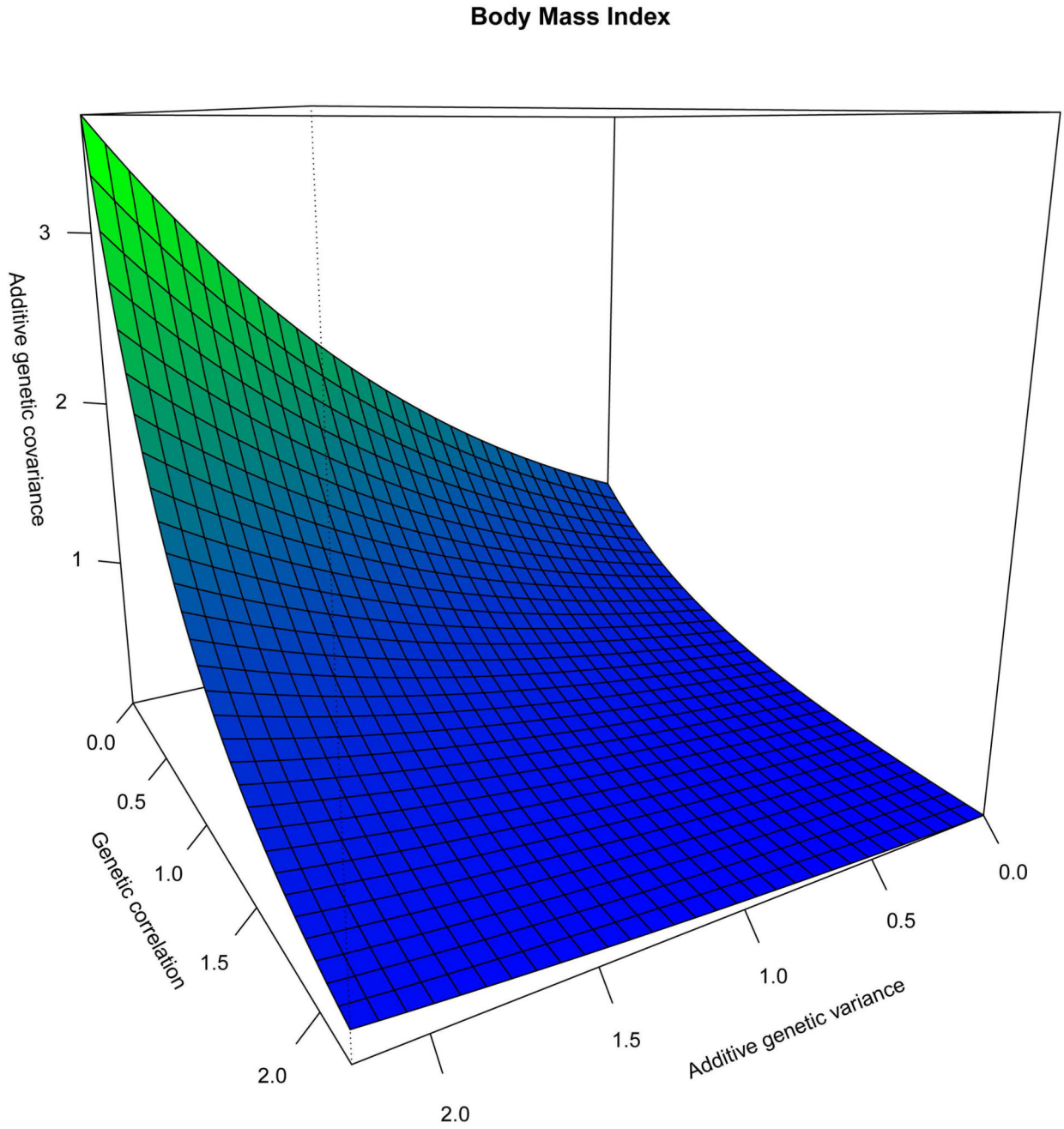

Figure 3.
Additive Genetic Covariance Function for BMI. The covariance function is here expressed as a joint function of the additive genetic variance and genetic correlation functions.

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Table 1

Characteristics of Subjects Including Environmental Measures and Heritabilities for Cardiometabolic Risk Factors in 617[a] SAFARI Children

Trait*	N[a]	Mean ± SD or %	Definitions/Normal Thresholds	Heritability h^2± S.E	p-value [b]	Variance explained by covariates (%)
Girls	617	48.8%	-	-	-	-
Age	617	11.7 ± 3.5	-	-	-	-
Overweight	617	53.8%	BMI ≥85 and <95th percentile	-	-	-
Obese	617	33.7%	BMI ≥95 and <99th percentile	-	-	-
Pre-diabetes	617	13.3%	FPG ≥100 and <126 mg/dl	-	-	-
Metabolic Syndrome[c]	617	18.6%	< 3 components of the 6 examined components	-	-	-
Harvard Physical Fitness Score (HPFS)	474	59.1 ± 24.8	> 96 excellent score	-	-	-
Sedentary Activity_Usual	606	0.67 ± 0.35	5 categories of time spent: 0 – 3hrs	-	-	-
Sedentary Activity_Yesterday	617	0.51 ± 0.31	5 categories of time spent: 0 – 3hrs	-	-	-
Body mass Index [BMI(kg/m^2)][d]	616	22.9 ± 6.4	BMI values at 6 &17 years[f]: Boys:16.9±0.26; 24.9± 0.70 Girls:16.0±0.25; 23.9 ±0.56	0.79 ± 0.12	5.1×10^{-11}	0.26
Waist Circumference (WC, mm)[d]	615	773.0 ± 180.4	WC values at 6 & 17 years[f]: Boys:57.4±0.74; 85.6±1.82 Girls:56.5±0.60; 82.2±1.50	0.67 ± 0.12	2.5×10^{-8}	0.36
Fat Mass (Kg)[d]	615	14.4 ± 15.9	Boys: 28–23% [g] Girls: 31–35%	0.57 ± 0.12	3.0×10^{-7}	0.36
Fasting Glucose (mg/dl)[d]	609	89.6 ± 7.1	< 100 mg/dl	0.43 ± 0.12	5.2×10^{-5}	0.02
Fasting Insulin (μIU/ml)[d]	600	13.0 ± 7.2	≤16.25 uIU/ml	0.64 ± 0.12	1.8×10^{-8}	0.12

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Trait*	N[a]	Mean ± SD or %	Definitions/Normal Thresholds	Heritability h^2± S.E	p-value [b]	Variance explained by covariates (%)
HOMA-IR[e]	599	1.9 ± 1.0	< 3 [h]	0.63 ± 0.12	1.0×10^{-7}	0.11
HDL (mg/dl)[d]	605	45.5 ± 10.5	> 45 mg/dl[i]	0.62 ± 0.12	2.0×10^{-7}	0.06
TG (mg/dl)[d]	602	73.6 ± 35.7	<75 mg/dl (0 to 9 yrs)[i] <90 mg/dl (10–19 yrs)[i]	0.75 ± 0.12	2.0×10^{-10}	0.04
SBP (mmHg)[d]	617	104.3 ± 9.7	BP <120/80 mmHg [j]	0.70 ± 0.11	1.0×10^{-10}	0.20
DBP (mmHg)[d]	617	63.1 ± 7.0	BP <120/80 mmHg [j]	0.58 ± 0.11	1.0×10^{-7}	0.08
Metabolic Syndrome Risk Score (# of MS Components (MSC)	617	1.28 ± 1.36	risk score range: 0–5	0.58 ± 0.13	3.2×10^{-6}	0.05

[a]Sample sizes for CMRFs varied from 599 (HOMA-IR) to 617 (MSC) based on availability of data and exclusion of outliers (i.e., values ± 4 SD from the mean were excluded from genetic analysis); Sample sizes for environmental variables ranged from 474 (Harvard fitness scores) to 617 (sedentary activity_ yesterday);

[b]From likelihood ratio tests of models with the additive genetic variance estimated and constrained to 0;

[c]As defined in Fowler et al. 2013;

[*]CMRF definitions and descriptions were provided in Fowler et al. 2013;

[f]BMI and WC (cm) Reference value ranges (mean ± Standard Error of the Mean[SEM]) for boys and girls at 6 and 17 years of age (Fryar, Gu, & Ogden, 2012);

[d]Traits were inverse-normalized for genetic analyses;

[e]homeostasis model of assessment-insulin resistance.

[g](C. L. Ogden, Li, Freedman, Borrud, & Flegal, 2011);

[h](Keskin, Kurtoglu, Kendirci, Atabek, & Yazici, 2005);

[i](Hauk, 2012);

[j](Chow et al., 2010).

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Table 2

Polygenic Model vs. Full G × E (Continuous) Interaction Models for CMRFs

Trait	Environment	Polygenic Model Vs. Full G × E Interaction Model			
		Model	Ln Likelihood	LR Test	p-value
BMI	HPFS	Polygenic	−246.2510		
		Full G × E	−243.0798	6.3424	0.069020 *
BMI	SA_y	Polygenic	−294.6440		
		Full G × E	−285.2698	18.7484	0.000015 *
WC	HPFS	Polygenic	−227.2178		
		Full G × E	−225.2784	3.8788	0.209321 *
WC	SA_u	Polygenic	−273.9042		
		Full G × E	−271.671	4.4664	0.161246 *
WC	SA_y	Polygenic	−281.8768		
		Full G × E	−280.343	3.0678	0.298495 *
FM	HPFS	Polygenic	−261.6764		
		Full G × E	−254−0216	15.3096	0.001022
FM	SA_y	Polygenic	−299.9619		
		Full G × E	−295.4529	9.0179	0.020032
FI	HPFS	Polygenic	−241.5861		
		Full G × E	−237.8490	7.4741	0.041025
FI	SA_y	Polygenic	−287.8721		
		Full G × E	−283.7673	8.2097	0.029182
HIR	HPFS	Polygenic	−235.3967		
		Full G × E	−232.1142	6.5650	0.062336 *
HIR	SA_u	Polygenic	−285.0120		
		Full G × E	−281.6945	6.6350	0.060366 *
HIR	SA_y	Polygenic	−286.9285		
		Full G × E	−283.7391	6.3789	0.067879 *

Genet Epidemiol. Author manuscript; available in PMC 2019 June 01.

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Trait	Environment	Polygenic Model Vs. Full G × E Interaction Model			
		Model	Ln Likelihood	LR Test	p-value
MSC	SA_u	Polygenic	−274.9191		
		Full G × E	−271.7375	6.3632	0.068369*
HDL	SA_y	Polygenic	−270.1281		
		Full G × E	−266.9251	6.406	0.06704*
DBP	SA_u	Polygenic	−296.7298		
		Full G × E	−293.1876	7.0845	0.049101

Poly = polygenic; LR = likelihood ratio;

*Examination of MLEs and their standard errors show that a reduced model may be important (see text)

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Table 3

Genotype by Environment (Continuous) Interaction Effects on CMRFs.

Trait	Environment	Mechanism	G × E Interaction Full or Reduced Models vs. Constraint Models			p-value*	power
			Model	LnL	LR Test		
BMI_HPFS	HPFS	Genetic Correlation	Red. G×E Model	−243.6020			
			Con_lambda	−246.2510	5.2981	0.0107[a]	0.7444
BMI_Say	SAy	Genetic Variance	Full G×E Model	−285.2698			
			Con_gamma	−289.8119	9.0842	0.0025[b]	0.8541
BMI_Say	SAy	Genetic Correlation	Full G×E Model	−285.2698			
			Con_lambda	−289.4178	8.296	0.0040[a]	0.8917
WC_HPFS	HPFS	Genetic Correlation	Red. G × E Model	−225.5523			
			Con_lambda	−227.2178	3.331	0.0340[a]	0.5718
WC_Sau	SAu	Genetic Correlation	Red. G×E Model	−272.0554			
			Con_lambda	−273.9042	3.6977	0.0272[a]	0.6097
WC_Say	SAy	Genetic Variance	Red. G × E Model	−280.984			
			Con_gamma	−281.877	1.7849	0.1815	0.2668
FM_HPFS	HPFS	Genetic Variance	Full G × E Model	−254.0216			
			Con_gamma	−258.7501	9.4570	0.0021[b]	0.8676
FM_Say	SAy	Genetic Correlation	Full G × E Model	−295.4529			
			Con_lambda	−296.4619	2.0179	0.0777	0.4123
FI_Sau	SAu	Genetic Variance	Red. G × E Model	−284.343			
			Con_gamma	−285.887	3.0895	0.0788	0.42
FI_Say	SAy	Genetic Variance	Red. G × E Model	−284.684			
			Con_gamma	−287.872	6.3756	0.0116[a]	0.714
HOMA-IR_Sau	SAu	Genetic Correlation	Red. G×E Model	−283.0792			
			Con_lambda	−285.0120	3.8656	0.0246[a]	0.6261
HOMA-IR_Say	SAy	Genetic Correlation	Red. G × E Model	−285.1387			
			Con_lambda	−286.9285	3.5796	0.0292[a]	0.5978

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Trait	Environment	Mechanism	G × E Interaction Full or Reduced Models vs. Constraint Models			p-value*	power
			Model	LnL	LR Test		
HOMA-IR_HPFS	HPFS	Genetic Correlation	Red. G × E Model	−233.6242			
			Con_lambda	−23b5.3967	3.545	0.0299[a]	0.5943
MSC_Sau	SAu	Genetic Correlation	Red. G × E Model	−273.2938			
			Con_lambda	−274.9191	3.2506	0.0357[b]	0.5631
HDL_Say	SAy	Genetic Correlation	Red. G × E Model	−268.7425			
			Con_lambda	−270.1281	2.7712	0.048[b]	0.5084
DBP_SAu	SAu	Genetic Variance	Red. G × E Model	−294.7716			
			Con_gamma	−296.7298	3.9164	0.0478[b]	0.5076

*from likelihood ratio (LR) tests of models with either the gamma or lambda parameters estimated and constrained (Con) to 0; (Con_gamma (γ) = genetic variance; Con_lambda (λ) = genetic correlation; Red. G × E model = reduced model;

[a]= significant after correcting for multiple-hypothesis testing;

[b]= significant and multiple testing is not needed because only one test was performed for this hypothesis.

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Table 4

mg-G × E (Continuous) Interaction Models for CMRFs

Trait	Environment/SNP	G × E Model vs. G × E Model with SNP			
		Model	Ln Likelihood	LR Test	p-value*
BMI	HPFs	G × E	−243.601971		
	rs1333049	mg-G × E	−234.296911	18.61012	1.6×10^{-05}
	rs16986921	mg-G × E	−236.050597	15.102748	1.0×10^{-04}
	rs12695382	mg-G × E	−234.814916	17.57411	2.8×10^{-05}
	SA_y	G × E	−285.269841		
	rs1333049	mg-G × E	−278.646201	13.24728	2.7×10^{-04}
	rs16986921	mg-G × E	−281.860341	6.819	9.0×10^{-03}
	rs12695382	mg-G × E	−280.859309	8.821064	3.0×10^{-03}
WC	HPFs	G × E	−225.552263		
	rs1333049	mg-G × E	−215.260173	20.58418	5.7×10^{-06}
	rs16986921	mg-G × E	−217.893680	15.317166	9.9×10^{-05}
	rs12695382	mg.G × E	−216.345399	9.206864	2.4×10^{-03}
	SA_u	G × E	−272.055371		
	rs1333049	mg-G × E	−264.180104	15.750534	7.2×10^{-05}
	rs16986921	mg-G × E	−268.201910	7.706922	5.5×10^{-03}
	rs12695382	mg-G × E	−266.696222	10.718298	1.1×10^{-03}
	SA_y	G × E	−280.98437		
	rs1333049	mg-G × E	−273.575208	14.818324	1.2×10^{-04}
	rs16986921	mg-G × E	−276.766953	8.434834	3.7×10^{-03}
	rs12695382	mg-G × E	−275.082909	11.802922	5.9×10^{-04}
FM	HPFS	G × E	−254.258788		
	rs1333049	mg-G × E	−245.938561	16.640454	4.5×10^{-05}
	rs16986921	mg-G × E	−247.401557	13.714462	2.1×10^{-04}
	rs12695382	mg-G × E	−247.328433	13.86071	2.0×10^{-04}

Trait	Environment/SNP	G × E Model vs. G × E Model with SNP			
		Model	Ln Likelihood	LR Test	p-value*
	SA_y	G × E	−295.452938		
	rs1333049	mg-G × E	−290.640463	9.624950	1.9×10^{-03}
	rs16986921	mg-G × E	−292.985805	4.934266	2.6×10^{-02}
	rs12695382	mg-G × E	−291.236897	8.432082	3.7×10^{-03}
FI	SA_u	G × E	−284.342451		
	rs1333049	mg-G × E	−280.948679	6.787544	9.2×10^{-03}
	rs16986921	mg-G × E	−283.886050	0.912802	0.3393721[a]
	rs12695382	mg-G × E	−281.444604	5.795694	1.6×10^{-02}
	SA_y	G × E	−284.684313		
	rs1333049	mg-G × E	−281.619929	6.128768	1.3×10^{-02}
	rs16986921	mg-G × E	−284.359511	0.649604	0.4202543[a]
	rs12695382	mg-G × E	−281.660447	6.047732	1.4×10^{-02}
HOMA-IR	HPFs	G × E	−233.624161		
	rs1333049	mg-G × E	−232.027806	3.19271	0.0739673[a]
	rs16986921	mg-G × E	−233.469271	0.30978	0.5778152[a]
	rs12695382	mg-G × E	−231.407711	4.43290	3.5×10^{-02}
	SA_u	G × E	−283.079218		
	rs1333049	mg-G × E	−280.748401	4.661634	3.1×10^{-02}
	rs16986921	mg-G × E	−282.714627	0.729182	0.3931485[a]
	rs12695382	mg-G × E	−280.560791	5.036854	2.5×10^{-02}
	SA_y	G × E	−285.138691		
	rs1333049	mg-G × E	−282.592845	5.091692	2.4×10^{-02}
	rs16986921	mg-G × E	−284.678495	0.920392	0.3373721[a]
	rs12695382	mg-G × E	−282.243916	5.789550	1.6×10^{-02}
MSC	SA_u	G × E	−273.293816		
	rs1333049	mg-G × E	−271.051664	4.484304	3.4×10^{-02}

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Trait	Environment/SNP	G × E Model vs. G × E Model with SNP			
		Model	Ln Likelihood	LR Test	p-value*
	rs16986921	mg-G × E	−271.921924	2.743784	0.0976333[a]
	rs12695382	mg-G × E	−272.280778	2.026076	0.1546194[a]
HDL	SA_y	G × E	−268.742515		
	rs1333049	mg-G × E	−267.394514	2.696002	0.1006002[a]
	rs16986921	mg-G × E	−267.246377	2.992276	0.0836625[a]
	rs12695382	mg-G × E	−268.714120	0.056790	0.7723941[a]
DBP	SA_u	G × E	−294.771576		
	rs1333049	mg-G × E	−287.273606	14.995940	1.1×10^{-04}
	rs16986921	mg-G × E	−289.493242	10.556668	1.2×10^{-03}
	rs12695382	mg-G × E	−291.119736	7.30368	6.9×10^{-03}

LR = likelihood ratio;

*Significant after multiple testing correction (FDR = 0.05) unless indicated by [a]

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