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Interactions of Genetic Variants with Physical Activity are Associated with Blood Pressure in Chinese: The GenSalt Study

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Abstract

Background—Blood pressure (BP) homeostasis involves complex interactions among genetic and non-genetic factors, providing major challenges to dissection of the genetic components that influence BP and hypertension. In this study, we examine the effects of interaction of genetic variants with physical activity on BP in a relatively genetically homogenous cohort of rural Chinese villagers.

Methods—Generalized estimating equations analysis was used to test for associations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with variants in 24 genes in BP pathways (196 SNPs) among 3,142 Chinese participants divided according to physical activity (active versus inactive groups).

Results—In the physically active group, 2 SNPs in NR3C2 were significantly associated with lower SBP, and a SNP in SCNN1B was significantly associated with lower SBP and DBP. In the physically inactive group, a SNP in APLNR was associated with lower SBP, a SNP in GNB3 was associated with higher SBP and DBP, and a SNP in BDKRB2 was associated with lower DBP.

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Conflict of interest: None

Cumulative effects in carriers of minor alleles of these SNPs showed reductions of SBP and DBP as large as 8 and 5 mmHg, respectively, in the active individuals compared to inactive individuals carrying the same number of minor alleles.

Conclusions—We found that physical activity modifies the effects of genetic variants on BP. However, our results also show that active individuals with specific genotypes always have lower BP than inactive individuals with the same genotypes, demonstrating the overall beneficial effects of physical activity on blood pressure.

Keywords

Blood pressure; Epidemiology; genetics; physical activity; gene by environment interaction

INTRODUCTION

High blood pressure (BP) or hypertension is a global health issue[1] and a major risk factor for cardiovascular, cerebrovascular, renal[2], and eye diseases[3]. Major risk factors for hypertension include physical inactivity, obesity, high sodium and low potassium diet, and alcohol consumption[2, 4]. Genetic factors also influence hypertension, likely via complex interactions among many genes, as well as interactions among genetic and environmental factors such as diet and physical activity.

Controlling high BP by medication and life style modification can have a substantial impact on avoiding or reducing its medical complications and end organ damage[5-8]. Increased physical activity is an important life style modification that is recommended for hypertension patients based on documented benefits in many randomized clinical trials and meta-analyses[9, 10]. Different physiological mechanisms have been proposed to explain the beneficial effects of physical activity on BP levels. Increases in cardiac output during physical activity to meet higher demands for oxygen cause increased arterial shear stress associated with enhanced release of nitric oxide, a potent vasorelaxant[11], and reduced expression of endothelin 1, a potent vasoconstrictor[12]. Physical activity also reduces plasma levels of norepinephrine and renin that are associated with reduced sympathetic nervous system activities and systemic vascular resistance[9]. Improved endothelial function and reduced insulin resistance are other characteristics of physical activity that might account for its beneficial effects on BP[9].

The search for genetic factors underlying hypertension and measures of BP has been difficult, in part due to the complexity of interactions with environmental factors such as physical activity. Previous studies have examined interactions of particular genetic variants with different forms of physical activity, but typically included limited numbers of variants and relatively small sample sizes[11-19]. In this study, we test for effects of interaction of genetic variation with physical activity on BP in large numbers of rural Chinese (n=3,142). The study population was comprised of Han Chinese families from six rural villages in Northern China that participated in the multicenter study “Genetic Epidemiology Network of Salt Sensitivity (GenSalt)”. We interrogated 24 genes from key metabolic and physiological pathways that regulate BP homeostasis using 196 SNPs selected from the

International HapMap project to provide comprehensive gene coverage in the Chinese population[20].

METHODS

Study population

The study subjects were Han Chinese families from six rural villages in Northern China that participated in the multicenter GenSalt study to identify genetic factors that influence BP response to sodium and potassium intake. Chinese families were recruited through 18-60 year old probands who were either prehypertensive or had stage 1 hypertension (SBP of 130-160 mmHg and/or DBP of 85-100 mmHg), but had never been on any hypertension medication. Family members were excluded if they had stage-2 hypertension, secondary hypertension, or were treated with antihypertensive medications or low sodium diets. Additional exclusions included history of cardiovascular disease, diabetes, pregnancy, or heavy alcohol drinkers. A total of 3,142 individuals in 631 families participated in the GenSalt study. A large number of demographic, anthropomorphic, and medical variables were measured in this population. More information about subject recruitment and study measurements are available elsewhere[21]. All the participants signed an informed consent, and the Institutional Review Board approvals for this study were obtained at all the participant institutions.

Measurements of Blood Pressure and physical activity

Prior to dietary interventions, GenSalt participants were measured for base line BP over a three-day period while consuming their usual diets. Three morning BP measurements on each of three days were taken by the same trained and certified technician using the same random-zero sphygmomanometer. The average of these 9 SBP measurements was used in this analysis. Information about the intensity and the duration of habitual physical activities during work and leisure was collected using a detailed questionnaire. A metabolic equivalent (MET) variable defined as the ratio of the metabolic rate while seated and resting to the metabolic rate while performing particular tasks, was calculated for each participant (weekday and weekend), according to the following formula:

$$MET\ (weekday/weekend) = (hours\ of\ vigorous\ activity) * 8 + (hours\ of\ moderate\ activity) * 4 + (hours\ of\ light\ activity) * 2 + (hours\ of\ sitting) * 2 + (hours\ of\ sitt$$

The average daily MET for each person was calculated based on the following formula:

$$Average\ MET = [MET\ (weekday) * 5 + MET\ (weekend) * 2] / 7\ days.$$

After adjustment for covariates (gender, age, age^2, and age^3), log transformed MET residuals were used to classify the participants as active (residual > 0) or inactive (residual ≤ 0).

SNP selection and genotyping

Lymphocyte DNA samples from GenSalt participants were genotyped for SNPs in genes in key pathways of BP regulation. Initially, 237 SNPs (26 genes) were selected based on linkage disequilibrium structure in the Chinese population in the international HapMap project[20]. High throughput SNP genotyping was performed using the ABI SNPlex platform according to the manufacturer's protocol[22]. 41 SNPs were excluded from subsequent association analysis due to low call rate (<80%), low minor allele frequency (MAF <0.05), or deviations from Hardy-Weinberg Equilibrium (HWE) ($p<0.001$). Supplementary Table 1 shows detailed information about the 196 SNPs in 24 genes that were used for association analysis.

Statistical analysis

Plink and PedCheck were used to assess consistency of the SNP genotypes with Mendelian transmission in GenSalt pedigrees[23, 24]. ASPEX and GRR were used to check for potential pedigree misreported relationships[25, 26]. Haploview was used for SNP descriptive statistics[27]. Generalized Estimating Equation methods (GEE) were used to test for associations between BP and genetic variants in active, inactive, and total populations under the additive model[28]. BP was adjusted for age, age^2, age^3, gender, body-mass index (BMI), pedigree generation, BP measurement room temperature and field center, and standardized to ensure a mean of 0 and a SD of 1. All SNPs were coded additively for the minor allele, and GEE analysis was performed with SAS 9.1 (proc genmod), and exchangeable working correlation matrix. False Discovery Rate (FDR) was used to correct for the multiple testing in GEE analysis[29]. Examining the LD patterns between the 196 SNPs showed that 24 pairs of SNPs were in almost complete LD ($r^2 \geq 0.90$), yielding 172 independent tests for our analysis.

RESULTS

A total of 3,142 individuals from rural Chinese families that participated in the GenSalt multicenter project were included in this study. Table 1 shows their basic characteristics stratified according to physical activity status (active versus inactive). The average age in both groups was 50 years old and there was slightly, but not significantly, more males in the active group compared to the inactive group. By design, the active group had significantly higher MET than the inactive group (mean MET scores differed by 30.6). In addition, the inactive group had significantly higher BP and BMI, while there was no significant difference in cigarette smoking and alcohol consumption between the two groups.

We genotyped the GenSalt subjects for DNA variants in 24 genes involved in metabolic and physiological pathways related to BP homeostasis. Figure 1 shows the results of association analysis in groups stratified according to physical activity status (complete list of 196 SNPs in Supplementary Table 1). We identified 6 SNPs in 5 genes (NR3C2, APLNR, GNB3, SCNN1B, BDKRB2) that were significantly associated in either the active or inactive groups ($p < 0.01$) (Table 2). Figure 2 shows mean adjusted effects on SBP and DBP for SNP genotypes that showed significant associations for active and inactive groups. SNP NR3C2-rs4835493 was not included in Figure 2 due to high LD with rs11099681 ($r^2 = 0.98$). In the

inactive group, the minor allele of APLNR-rs2282623 was associated with reduced SBP, the minor allele of BDKRB2-rs945039 was associated with reduced DBP, and the minor allele of GNB3-rs4963516 was associated with elevated SBP and DBP. In the active group, the minor allele of NR3C2-rs11099681 was associated with reduced SBP, and the minor allele of SCNN1B-rs7205273 was associated with reduced SBP and DBP. The FDR for all significant p-values was 0.37, meaning that less than 3 of the significant SNPs might be false positive results.

Figure 3 shows combined genotypic effects on SBP and DBP in subjects carrying increasing numbers of minor alleles for the significant SNPs according to physical activity status. Within the inactive group, subjects did not show consistent effects on SBP and DBP with increasing numbers of minor alleles. In contrast, individuals within the active group showed reduced SBP and DBP with increasing numbers of minor alleles. Active individuals carrying >4 minor alleles have up to 8 mm lower SBP (Panel A), and those with >3 minor alleles have up to 5 mmHg lower DBP (Panel B) compared to inactive individuals carrying the same number of minor alleles (Figure 3).

DISCUSSION

The purpose of this study was to investigate effects of interactions between genetic variation and physical activity on BP in rural Chinese participants of the multicenter GenSalt study (n=3,142). Of 196 SNPs across 24 genes from physiological pathways that regulate BP homeostasis, we identified SNPs at five loci (NR3C2, APLNR, GNB3, SCNN1B, BDKRB2) that showed significant associations with BP in either the active or inactive groups (Figure 1, Table 2). Our results provide evidence for effects of interactions between SNPs and physical activity on BP, with demonstrable differences in individual SNP effects according to physical activity status (Figure 2).

In the physically active group, two correlated intronic SNPs (rs11099681 and rs4835493) in NR3C2 (nuclear receptor subfamily 3, group C, member 2) were significantly associated with SBP. NR3C2 encodes the mineralocorticoid receptor that is activated by binding with aldosterone and cortisol, leading to higher BP via alteration of renal sodium retention, expression of nitric oxide synthase and vascular endothelin 1, and vasoconstrictor sensitivity to catecholamines[30]. We also found a SNP (rs7205273) in the first intron of SCNN1B (sodium channel, nonvoltage-gated 1, beta subunit) that showed significant associations with SBP and DBP in the physically active group. Interestingly, the SNPs that showed significant associations in the physically active group are located in genes that also contain rare mutations that cause monogenic hypertension. Previous studies have found that rare NR3C2 variants cause monogenic forms of hypertension, including autosomal dominant pseudohypoaldosteronism[31]. Mutations in SCNN1B cause Liddle's syndrome and pseudohypoaldosteronism type I (PHA I)[32]. Taken together, our results suggest that common variants in such genes that contain mutations causing monogenic disorders may also influence blood pressure homeostasis in the general population under particular contexts such as physical activity.

In the physically inactive group, we found significant association with SBP for rs2282623 in the 3' untranslated region (potential regulatory region) of APLNR (apelin receptor) that encodes APJ, a G protein-coupled receptor. The apelin/APJ system plays a role in cardiovascular homeostasis, vascular tone, and cardiac contractile function. This system regulates BP via nitric oxide mediated mechanisms[33], and is involved in energy balance and obesity[34]. In spontaneously hypertensive rats, exercise training decreased SBP and substantially lessened pathological cardiac hypertrophy via increased expression of the apelin/APJ system[35]. In addition, we found a SNP (rs4963516) in the 5' flanking region (potential regulatory region) of GNB3 (guanine nucleotide binding protein, beta polypeptide 3) that was significantly associated with SBP and DBP in the physically inactive group. This subunit of the heterotrimeric G protein plays a role in sodium retention by altering activities of sodium exchange across cellular membranes leading to changes in BP[36]. Signal transduction via G proteins is also important for adipocyte formation[37]. Previous studies of GNB3 have reported associations of rs5443 with hypertension[38] and obesity[37]. Interactions of GNB3 rs5443 and BP response to an exercise training program were identified in African American women[18]. This variant was also found to interact with obesity and physical activity in hypertension in African Americans[19]. However, we did not find association of GNB3 rs5443 with blood pressure measures and interaction with exercise in the GenSalt cohort. We also found an intronic SNP (rs945039) in BDKRB2 (bradykinin receptor B2) that was significantly associated with DBP in the physically inactive group. Bradykinin plays a central role in physiological pathways of vasodilation and insulin sensitivity. Other BDKRB2 variants have shown associations with physical performance in track athletes (efficiency of skeletal muscle contraction and endurance)[39].

Many previous studies have investigated interactions between genetic variants and different forms of exercise or physical activity on BP traits[11-19]. Several such studies have used an intervention training program or physical activity monitoring to test how BP response differs based on an individual's genotype at specific loci[14, 15, 17, 18]. Like these previous studies, our findings of significant genetic associations do not imply that physical activity is not useful for individuals with any particular genotype given the overall beneficial effects of physical activity on BP traits, as well as numerous other well-documented health benefits. We found that active individuals with specific genotypes always have lower BP than inactive individuals with the same genotypes (Figure 2). However, genetic information can help identify individuals where physical activity is not sufficient to control their BP, requiring other BP lowering interventions[14]. In addition, identification of particular genes and genetic variants that are associated with BP help further our understanding of the pathophysiology of BP regulation and the etiology of hypertension. Characterization of interactions between genetic variants and physical activity is also important to understand the mechanisms of how physical activity lowers BP measures, ultimately contributing to improved medications and better hypertension treatment modalities.

We recruited our study participants from a semi-isolated Han Chinese population to minimize genetic and environmental heterogeneity. No subjects were under any form of BP treatments to avoid all complications associated with controlling for drug response, and to ensure better BP measurements. The participants provided subjective assessments of their physical activity using questionnaires that are susceptible to recall bias. However, the effects

should be minimal since this is a farming community with a routine and repetitive life style that should facilitate accurate recall. Future studies in other cohorts will be required to replicate these associations of genetic variants that interact with physical activity to influence SBP and DBP.

In conclusion, this study provides evidence that interactions between genetics variants and physical activity play a role in BP regulation. However, we found that effects of physical activity can be stronger than genetic effects, indicating that physical activity should continue to be recommended for hypertensive patients, regardless of their genetic makeup.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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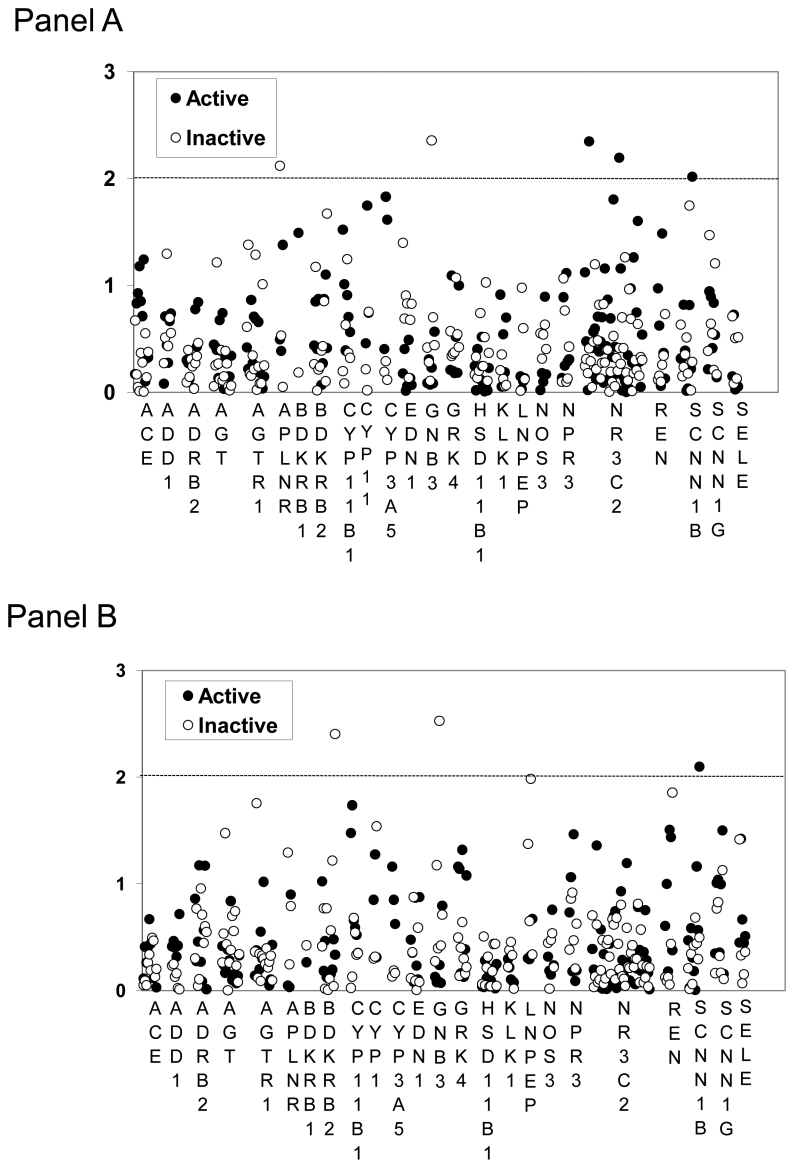

Figure 1.

−log p-values (Y axis) for associations of SBP (Panel A) and DBP (Panel B) with 196 individual SNPs separately for the physically active group and the physically inactive group of rural Chinese participants (n=3,142). The name of each of the 24 genes from blood pressure pathways is presented below graph (X axis). The dotted lines indicate p value <0.01.

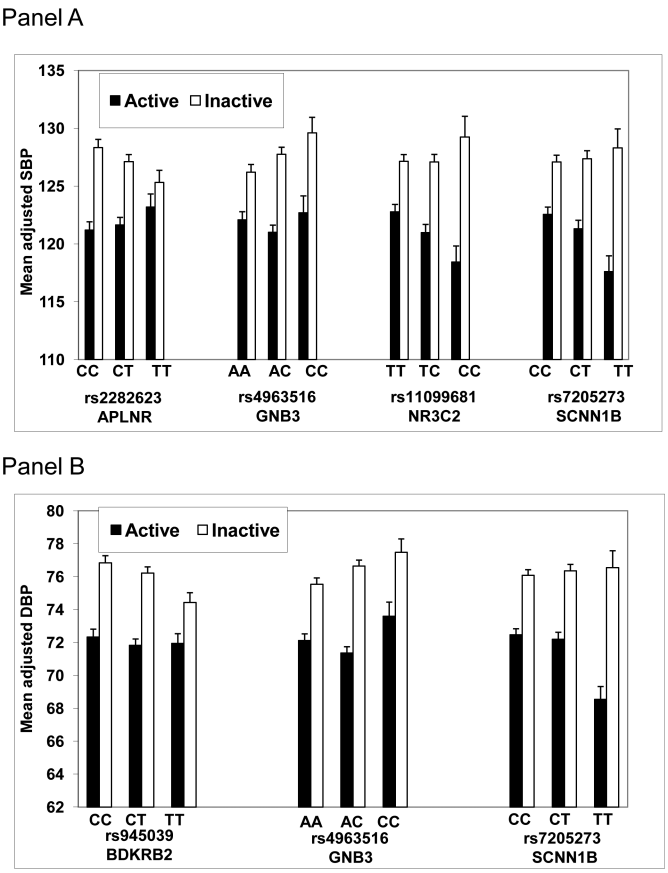

Figure 2.

Mean adjusted SBP (Panel A) and DBP (Panel B) (with standard errors) for each genotype for significantly associated SNPs ($p<0.01$) separately for the active group and the inactive group. Each gene, SNP number, and SNP genotype are presented below the graph.

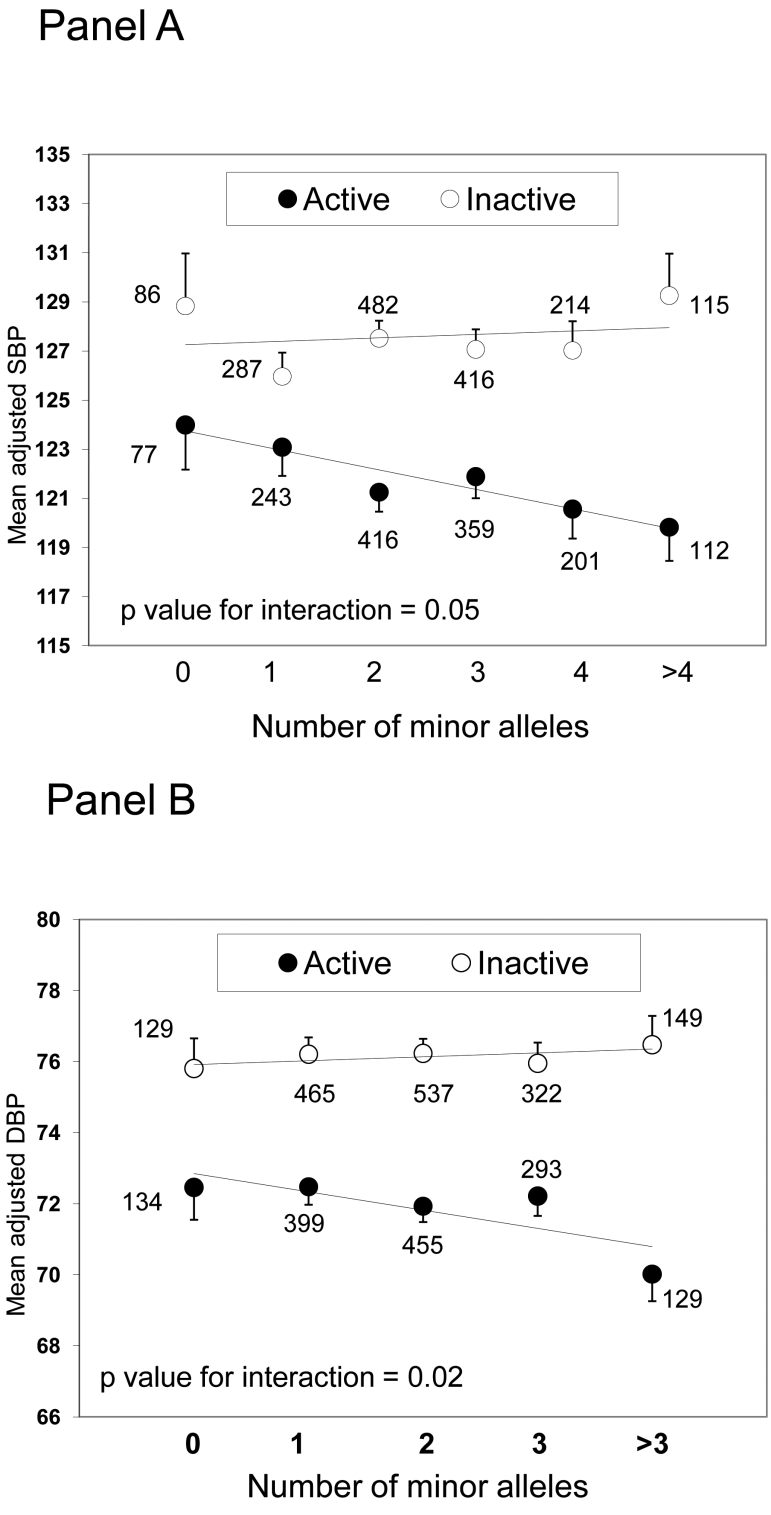

Figure 3.

Cumulative effects of the minor alleles for all of the significant SNPs on the values of mean adjusted SBP (Panel A) and DBP (Panel B). The best fitting trend lines for each group and

the p values interactions are presented. The numbers of individuals are shown next to each point.

Table 1

Basic characteristics of the GenSalt participants (active and inactive groups).

	Active	Inactive
N*	1453	1689
Male %	53.6	49.2
Age	50.1 ± 16.8	50.0 ± 16.7
BMI*	22.8 ± 3.1	23.3 ± 3.3
SBP*	122.8 ± 20.4	126.1 ± 21.2
DBP (mmhg)*	73.0 ± 10.4	75.2 ± 11.1
MET*	73.1 ± 20.0	42.5 ± 10.0
Smoke %	16.3	18.2
Alcohol %	13.0	13.8

BMI: Body mass index

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

MET: Metabolic equivalent score

* $p<0.0001$ for comparisons between physically active and inactive groups

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Table 2

Results of stratified analyses for individual SNPs that are significantly (p<0.01) associated with SBP (A) and DBP (B) in either physically active or inactive groups.

(A)

Gene	SNP	Region	MAF	Maj/Min	Active β *	Active SE	Active p	Inactive β	Inactive SE	Inactive p	Combined β	Combined SE	Combined p
APLNR	rs2282623	3' UTR	0.40	C/T	0.043	0.044	0.320	−0.102	0.038	**0.008**	−0.040	0.030	0.185
GNB3	rs4963516	5' near gene	0.33	A/C	0.024	0.044	0.591	0.113	0.040	**0.004**	0.077	0.031	0.012
NR3C2	rs11099681	intron	0.29	T/C	−0.124	0.044	**0.005**	0.037	0.043	0.389	−0.048	0.031	0.123
NR3C3	rs4835493	intron	0.29	C/T	−0.120	0.044	**0.006**	0.037	0.043	0.385	−0.047	0.032	0.138
SCNN1B	rs7205273	intron	0.26	C/T	−0.111	0.043	**0.009**	0.029	0.045	0.519	−0.045	0.032	0.163

(B)

Gene	SNP	Region	MAF	Maj/Min	Active β *	Active SE	Active p	Inactive β	Inactive SE	Inactive p	Combined β	Combined SE	Combined p
BDKRB2	rs945039	intron	0.43	C/T	−0.029	0.039	0.462	−0.108	0.037	**0.004**	−0.072	0.027	**0.008**
GNB3	rs4963516	5' near gene	0.33	A/C	0.024	0.043	0.576	0.126	0.043	**0.003**	0.086	0.030	**0.005**
SCNN1B	rs7205273	intron	0.26	C/T	−0.108	0.041	**0.008**	0.044	0.044	0.319	−0.036	0.031	0.235

MAF: minor allele frequency

Maj/Min: Major/Minor allele

UTR: untranslated region

SE: standard error

p: p value.

β: beta coefficient

* effect size shown as beta coefficient in SD units for the minor allele.