Influence of the -3826A/G Polymorphism *UCP1* (rs1800592) and Physical Activity on Obesity-related Traits in Russian Females with Different Level of Physical Activity

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Abstract: The association between level of physical activity and -3826A/G polymorphism *UCP1* (rs1800592) with obesity-related traits was examined in the group of Russian females. A cross-sectional study of 124 adult females aged of 18-30 years living in Moscow was performed. The genotype of the *UCP1* rs1800592 variant was determined. Height, body mass, waist, hip circumferences and body fat mass were measured. Waist to hip ratio (WHR), waist to height ratio (WHtR), body mass index (BMI), and body adiposity index (BAI) were calculated. Association analysis revealed that physical activity and the -3826A/G polymorphism of *UCP1* (rs1800592) were significantly associated with obesity-related traits. However, physical activity had a greater impact on obesity-related traits. Decreased level of physical activity is associated with increased waist to height ratio, the amount of body fat and body adiposity index. Decreased level of physical activity enhanced the effect of *UCP1* gene polymorphism rs1800592 on obesity-related traits in the studied cohort.

1 INTRODUCTION

Over the last 50 years, the prevalence of obesity among adults increased dramatically. According to the last World Health Organization (WHO) report, the number of overweight and obese individuals 18 years and older raised to 39% and 13%, respectively.

Obesity is defined as a multifactorial disease which results from a combination of energy imbalance, low physical activity and genetic predisposition.

It was shown that the genetic effects may be modified by various environmental factors (Kilpeläinen et al., 2011; Rask-Andersen et al., 2017; Bondareva et al., 2019). Physical activity, diet, alcohol consumption, smoking, could enhance or attenuate the influence of genetic factors on obesity-related traits. For instance, physical activity attenuated the effect of *FTO* common variants on obesity risk (Kilpeläinen et al., 2011; Rask-Andersen et al., 2017; Bondareva et al., 2019). Several studies reported that the influence of other obesity-related loci is diminished by physical activity. In physically active adults, the minor T allele of the *UCP3* rs1800849 (-55C/T) variant is associated with a lower risk of obesity compared to C allele (Alonso et al., 2005). Physical activity attenuated the influence of the risk C allele of the *UCP1* rs3811791 on type 2 diabetes risk (Dong et al., 2020).

Gene-lifestyle (gene-environment) interactions can explain much of the variation in obesity-related traits. The identification of gene-lifestyle interactions is a promising method for understanding the etiology of obesity and development of preventive strategies (Lin et al., 2013).

In the current study, we investigate the effect of physical activity level along with the common variant of the *UCP1* rs1800592 (-3826A/G) on obesity-related traits in the female adults.

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2 MATERIALS AND METHODS

The study cohort included 124 healthy normal weight Russian females aged 18-30 years with different level of physical activity. The dataset included Russian females who live in Moscow metropolitan area. The average age of individuals was 18.1±4.2 and 18.4±0.9 years in physically active and inactive individuals, respectively. The study cohort included individuals with low physical activity level (N=54) and professional athletes (N=70) who are engaged in aerobic sports. The individuals in the first group performed less than 150 minutes of moderate or vigorous physical activity per week. Professional athletes were included in the second group with a high physical activity level. Physical activity level was determined by a short questionnaire in which subjects were asked about the number of minutes of moderate (moderate physical effort) or vigorous (hard physical effort) physical activity per week.

The study was approved by the Commission on Bioethics of the Biological Faculty of Lomonosov Moscow State University (Ref. 91-o from 24.05.2018). Each participant provided written informed consent before the examination. The examination was conducted at the Research Institute and Museum of Anthropology of Lomonosov Moscow State University. The anthropometric examination included measurements of height (cm), body weight (BW, kg), waist circumference (cm) and hip circumference (cm). Height and weight were measured by stable stadiometer Seca (SECA, Germany) and flat scale Seca (SECA, Germany). The following anthropometric indices were calculated: body mass index (BMI, kg/m2), body adiposity index (BAI, %), waist to hip ratio (WHR), waist to height ratio (WHtR) The percentage of body fat mass was measured by a bioimpedance analyzer ABC-01 “MEDASS” (Russia).

All genetic analysis was performed by commercial company Lytekh (Moscow, Russia). DNA was extracted and purified from buccal epithelium following the manufacturer’s procedures (COrDIS Sprint). The rs1800592 was determined using matrix-assisted laser desorption/ionization - time of flight mass spectrometry (MALDI-TOF MS). The genotype data was checked for Hardy-Weinberg equilibrium (HWE).

Statistical analysis was performed in the computer environment R, version 3.5.1 (RStudio Team, 2015). A comparison of the allele and genotype frequencies rs1800592 between two studied groups was carried out using the Fisher exact test (Raymond M., Rousset F., 1995). A standard exploratory analysis was carried out (Shapiro and Wilk, 1965; Grubbs, 1969; Levene et al., 1960). Based on the results of the exploratory analysis, we decided to use quantile regression (Koenker et al., 2001). Quantile regression has a few advantages compared to ordinary least square regression. Quantile regression is robust to outliers and does not require normality assumption. Moreover, here, the upper conditional quantiles functions were of interest. It is assumed that the effect of the rs1800592 of the *UCP1* will be stronger at higher values of the dependent variables. The models were built using quantreg package (Available at: https://CRAN.R-project.org/package=quantreg was used to build the regression model. Accessed: 07/08/2020). The bootstrap algorithm was used to calculate the standard error of the quantile regression model. Regression models were constructed for quantiles 10, 20, 30, 40, 50, 60, 70, 80, 90 to test the main effect of physical activity and the variant rs1800592 of the *UCP1* on the dependent variables. The main effect of the variant 1800592 *UCP1* on obesity-related traits was tested in the whole study population as well as in physically active (N=54) and inactive individuals (N=70). The dominant model was used (AG+GG vs AA). The main effect of physical activity was tested in the whole sample (N=124). The model was used to test the combined effect of the risk rs1800592 variant of the *UCP1* and physical activity. Age was added to the models as covariates. The Benjamini-Hochberg method was used for multiple testing comparison.

3 RESULTS AND DISCUSSION

The baseline phenotypic characteristics of the individuals are presented in the table 1 and figure 1.

The minor allele frequency of the variant *UCP1* rs1800592 (G allele) in the studied sample was 0.25. In European populations, minor allele frequency ranged from 0.15 to 0.27. The distribution of the rs1800592 *UCP1* in the study sample was in Hardy-Weinberg equilibrium (χ^2=0.31, p=0.57). Physically active and inactive individuals did not significantly differ in the allele frequency of the *UCP1* rs1800592 (p=0.14).

Quantile regression revealed that physical activity had a significant effect on obesity-related traits (Table 1). Individuals with a low level of physical activity had significantly higher body adiposity index (ß=4.16, $p=2*10^{-4}$), waist to height ratio (ß=0.01, $p=1*10^{-3}$) and the percentage of body fat mass (ß=6.30, $p=1*10^{-4}$). The influence of physical activity was higher at the upper quantile of waist to height

ratio, waist to hip ratio, and body adiposity index (Fig. 2). Low level of physical activity led to increase in waist to height ratio value by 0.01 at 25% quantile, by 0.02 at 50% quantile (median) and by 0.04 at 90% quantile (Fig. 2).

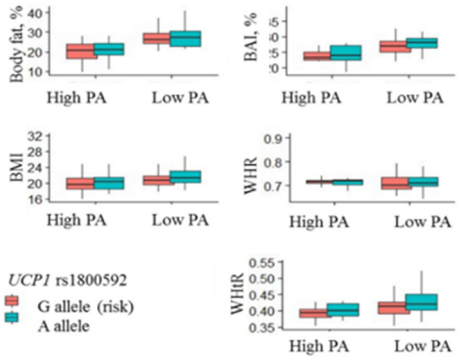

Figure 1: Boxplots of body fat percentage, body adiposity index (BAI), body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) in physically active inactive individuals according to rs1800592 *UCP1* risk allele (AG+GG vs AA).

Insufficient physical activity increased the amount of body fat. The influence of insufficient physical activity is higher at the lower quantiles (Fig. 2). Moreover, a low level of physical activity led to decrease in the amount of muscle mass (49.60% vs 51.1%, ß =-1.14, $p=3*10^{-3}$).

Table 1: Baseline phenotypic characteristics of the studied cohort (Mean, SD).

Parameter	Physically active (n=54)	Physically inactive (n=70)
Age	18.1 (4.2)	18.4 (0.9)
Waist circumference, cm	65.8 (3.8)	69.2 (6.0)
Hip circumference, cm	90.9 (4.7)	96.5 (5.8)
Body weight, kg	56.3 (7.1)	57.7 (7.3)
Height, cm	165.2 (7.2)	163.7 (5.7)
BMI, kg/m^2	20.6 (2.2)	21.6 (2.8)
Body fat content, %	20.3 (4.8)	28.1 (4.8)
Body adiposity index, %	25.1 (3.6)	28.1 (3.5)
Waist to hip ratio	0.72 (0.03)	0.72 (0.04)
Waist to height ratio	0.40 (0.03)	0.42 (0.04)
Muscle mass, %	50.5 (2.1)	48.6 (1.4)

Body mass index did not significantly differ between physically active and inactive individuals (ß=0.84, p=0.07). Anthropometric indices such as waist to height ratio and body adiposity indices may be better predictors of body fat accumulation in individuals with different levels of physical activity than body mass index (Sayeed et al., 2003; Lee et al., 2008). In physically active individuals, an increase in body mass index may be due to an increase in the muscle mass rather than fat mass (Freedman et al., 2005; Torstveit et al., 2012).

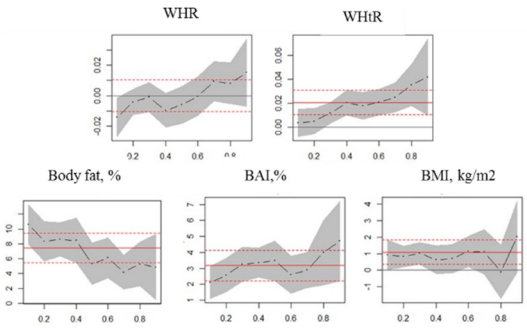

Figure 2: Changes of the beta (ß) value of the coefficients (in y-axis) at different quantiles (in x-axis) of body fat percentage, body adiposity index (BAI), body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) according to physical activity level.

In the studied sample, the risk G allele (AG+GG vs AA) of the *UCP1* rs18008592 was associated with a higher body mass index (ß=1.89, p=0.04), waist to hip ratio (ß=0.05, p=0.01), and waist to height ratio (ß=0.05, p=0.05). Several studies reported that the risk G allele increased the risk of obesity in different populations (Cha et al., 2008; Chathoth et al., 2018).

In physically inactive individuals, the risk G allele increased waist to height ratio, body mass index, the percentage of body fat mass and waist to hip ratio (table 2). In physically active individuals, the significant effect of the risk variant *UCP1* rs1800592 on waist to hip ratio (ß=0.03, p=0.05) and waist to height ratio (ß=0.01, p=0.01) was confirmed at the upper quantiles (table 2).

Physical activity and the *UCP1* rs1800592 risk variant significantly modified the risk of body fat accumulation. However, physical activity has a greater influence on obesity-related traits compared to the *UCP1* rs180592 risk variant. Physical activity modified the influence of the *UCP1* 1800592 risk variant on obesity-related traits. The influence of the *UCP1* rs180592 risk variant on obesity-related traits was higher in individuals with a low level of physical activity compared to physically active individuals. Several studies reported that physical activity is an effective way to control weight gain even in individuals with genetic predisposition (Kilpeläinen et al., 2011; Young et al., 2016; Rask-Andersen et al.,

2017; Bondareva et al., 2019). For instance, the risk *FTO* rs9939609 had a significant effect on body fat accumulation only in individuals with a low level of physical activity (Bondareva et al., 2019).

Table 2: Association of the risk G allele of the rs1800592 *UCP1* and obesity-related traits in physically active and inactive females (ß – regression coefficient, * - p-value<0.05, ** - p-value<0.01, Q- quantile).

Q	BF	BMI	WHR	WHtR	BAI
Physically inactive individuals					
0.1	0.54	0.17	0.01	0.01	1.4**
0.2	0.95	0.4	0.02	0.02*	1.51*
0.3	0.51	0.97*	0.01	0.01	1.97*
0.4	1.26	0.76*	0.00	0.01	2.2*
0.5	1.65*	0.48	0.00	0.01	1.64*
0.6	1.41	1.18	0.00	0.01	1.24
0.7	2.63**	1.94**	0.01	0.03**	1.07
0.8	2.44**	2.09**	0.02	0.02*	0.49
0.9	6.13*	3.31**	0.04	0.07**	1.47
Physically active individuals					
0.1	3.73*	0.03	0.001	0.01	1.55*
0.2	2.56*	0.01	0.001	0.001	-0.7*
0.3	0.31	0.01	0.001	0.001	0.32
0.4	0.85	0.01**	0.001	0.001	0.37
0.5	-0.22	0.66	0.001	0.01	0.65
0.6	0.03	0.6	0.001	0.01	0.59
0.7	0.29	0.8*	0.001	0.01	1.51
0.8	1.48	0.46	0.01	0.02**	1.65
0.9	0.10	1.30	0.01	0.03*	1.18

The study has several limitations. First, the *UCP1* rs1800592 risk variant explained a small amount of the variance of the obesity-related traits. Thus, it cannot be a significant predictor of obesity. However, recent study revealed around 1000 common obesity-related loci accounted for 6% of the variance of obesity-related traits (Yengo et al., 2018). Second, the studied sample included only female individuals, so the findings are not generalizable to other population, i.e. male. Third, the conducted study is cross-sectional, that does not take into account changes across the life course.

4 CONCLUSIONS

Physical activity and the *UCP1* rs1800592 risk variant significantly influence the risk of fat accumulation and obesity. However, physical activity is a better predictor of fat accumulation and obesity compared to the *UCP1* rs1800592 risk variant. However, to confirm the effect of the interaction, additional studies are needed in adult males, as well as in the group of children and adolescents.

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