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The Effect of Fto Gene Variant (rs17817449) and Menopause on Blood Pressure in Hypertensive and Normotensive Slovak Women

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ABSTRACT

This cross-sectional study examines the effect of fat mass and obesity-associated gene polymorphism (FTO) and menopause on blood pressure in Slovak midlife women. We assessed a total of 575 women ranging in age from 39 to 65 years. Data were analyzed using the univariate analysis of covariance to test the effect of risk FTO gene variant (G allele) and menopausal status (MS) on blood pressure in the hypertensive (HT) and normotensive (NT) women groups. A significant association was recorded between studied FTO gene variant and DBP (diastolic blood pressure) but only in HT women group (p = 0.044). Women possessing at least one risk allele (GG or GT) had slightly higher mean values of DBP than those without this allele. In the next step, our results showed a statistically significant association between MS and the FTO genotype and their common effect on SBP in NT women group (p = 0.002). The late pre-, perimenopausal G- allele carriers had lower SBP values in comparison with TT genotype carriers (estimated marginal means, 116.9 vs. 122.9 mm/Hg), while postmenopausal G- allele carriers had higher SBP values compared to TT genotype carriers (estimated marginal means, 120.7 vs. 114.1 mm/Hg). We did not notice any significant associations between FTO, menopause and DBP. Our findings indicate that FTO rs17817449 along with menopause are significant factors associated with systolic blood pressure in Slovak normotensive women.

Key words: *fat mass and obesity associated gene, hypertension, obesity indices, SNP, genetic polymorphism, medical anthropology*

Introduction

Global hypertension (HT) still presents a serious health burden, with nine million people dying annually from hypertension-related complications. HT is a complex trait supported by multifactorial genetic inheritance and environmental factors[1,2]. Although menopause[3,4], anthropometric characteristics and lifestyle factors, such as low physical activity and high-fat food intake, have been widely studied, genetic factors also play a critical role in HT development[5–7]. Many cohort studies have revealed that 30 – 50% of HT variability is genetically determined[8–10]. The fat mass and obesity-associated gene (FTO; ID 79068, OMIM accession number 610966) is composed of nine exons which span over 400 kb on chromosome 16[11–13]. Polymorphisms in the first intron of the FTO gene are significantly associated with an increased risk of adverse metabolic traits, including low HDL-C, high liver enzymes, diabetes, HT, and metabolic syndrome[14,15]. A number of studies have demonstrated a close correlation between FTO gene variants rs9939609, rs1421085, and rs17817449 and the occurrence of obesity and BMI in both children and adults[16–23]. Since obesity is one of the major risk factor for HT, it is necessary to explore the FTO gene's role in blood pressure regulation. The polymorphic sites, however, differ in different countries, ethnic, and age groups[24]. Dina et al.[16] reported that the GG genotype and the G allele of FTO variant rs17817449 (G > T in first intron) are strongly associated with the obesity phenotype in adults and children of European ancestry. The genetic variant was shown to be associated with BMI in the Western European[25,26] and North American European ancestry populations[11,16,27]. While a significant association of SNP with increased BMI was reported in the Korean population[28], no association was recorded in the Chinese[29], Japanese[30], or African American populations[31]. Moreover,

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Pausova et al's study[32] in a French-Canadian population suggested that FTO increases the risk not only of obesity but also of HT. The meta-analysis of He et al.[18] confirmed that FTO genotype mediates obesity-related hypertension. All of the above data indicate that the FTO gene variants could be genetic factors influencing blood pressure in various ethnic and age groups, including white women of European ancestry. Therefore, the purpose of the present study was to determine the relationship between FTO variant and blood pressure in adult Slovak women in age from 39 to 65 years. Furthermore, we analyzed gene-menopause associations with adjustment for potential confounding factors elevating blood pressure in women, including anthropometric parameters.

Material and Methods

Participants

The investigated sample comprised 575 white women of European ancestry, ranging in age from 39 to 65 years, from different localities in Slovakia. The women were divided into two groups on blood pressure status; women suffering from HT (255 participants; mean age 52.43 ± 6.10 years) and normotensive women (NT; 320 participants; mean age 47.44 ± 5.29 years), and also into WHO defined pre-, peri- and postmenopausal women. The premenopausal group consisted of women who had experienced regular menstruation during the last 12 months, and this continued at the time of the study. The perimenopausal group contained women who reported that their menstrual cycle length had become more irregular in the preceding 12 months or that they had stopped menstruating for between 3 and 12 months, and women were considered postmenopausal if they reported 12 consecutive months of amenorrhea prior to the examination[33]. Due to the low number of perimenopausal women, this group was amalgamated with premenopausal women. These divisions established 305 (53.0%) women in pre-/perimenopause and 270 (47.0%) in postmenopause. The study was performed in cooperation with general practitioners in western and central Slovak areas. Participants were interviewed during their regular checkups by a medical doctor. All women gave written Informed consent to participate in the study which adhered to the Declaration of Helsinki principles.

Anthropometric and body composition analysis

Anthropometric measurements were taken using standard anthropometric techniques by trained anthropologists. The following values were considered optimal; less than 24.9 kg/m^2 for body mass index (BMI), calculated as body weight in kilograms divided by height squared[34]; values below 0.80 for Waist-to-hip ratio (WHR) calculated as the circumference of the waist divided by the circumference of the hips[35] and less than 0.48 for Waist-to-height ratio (WHtR) calculated as the circumference of the waist divided by height squared[36].

Body composition measurements were performed in the morning after overnight fasting using a bioelectric impedance analyzer (BIA 101, Akern S.r.l.) at a signal frequency of 50 kHz and 800µA constant excitation current in a four-electrode arrangement. Detailed body composition variables were then obtained by the two specific measurements of resistance and reactance revealed by the software Bodygram programme (Version 1.21, Akern S.r.l)[37].

Incident HT was defined by systolic blood pressure (SBP) ≥ 140 and/or diastolic blood pressure (DBP) ≥ 90 mmHg at follow-up health examinations or a self-report of receiving treatment for high BP and/or a physician's diagnosis of hypertension during the follow-up period[38].

Genetic analysis

DNA was extracted from peripheral blood samples or buccal swabs by the SiMaxTM Genomic DNA Extraction Kit; and the FTO gene rs17817449 SNP variant was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using the method described by Bencova et al.[14]. Amplicons (198 bp) were then digested overnight by AlwNI restriction enzyme, and the fragments were separated by electrophoresis on 3% agarose gel. Running the final products on 3% agarose gel provided the G allele which formed an uncut PCR product of 198 bp, and the T allele produced two 99bp fragments.

Statistical analysis

Statistical analyses were performed using IBM SPSS for Windows (Statistical Package for the Social Science, version 20.0, Chicago, IL) and continuous data was expressed as mean ± SD, and a two-tailed p-value equal to or less than 0.05 was considered significant. Differences in the anthropometric and body composition characteristics between women with and without hypertension were tested using univariate analysis of covariance, with age as the covariate, and the Kolmogorov–Smirnov test checked data distribution normality. The resultant genotype frequencies were tested for deviation from the Hardy-Weinberg equilibrium by chi-square goodness of fit. The contingency tables with the chi-square independence test were used to analyze the differences in genotype distribution in the compared groups. A discriminant stepwise analysis model then determined variables identifying HT, and it also assessed each variable´s contribution to HT. All the measured anthropometric and body composition variables were included in discriminant analysis. Finally, the univariate analysis of covariance with control for age and WHtR was used to test the effect of risk FTO gene variant (G allele) and menopausal status (MS) on BP in the HT and NT women groups.

Results

The study participants' basic anthropometric parameters, obesity indices, and bioelectric impedance variable values are summarised in Table 1. The HT and NT women groups differed significantly in their mean ages ($p < 0.001$, 47.4 ± 5.29; y and 52.4 ± 6.10; y) and therefore all statistical comparisons of the quantitative variables were adjusted for age. All included variables, except those for body height, fat-free mass (%) and muscle mass (%) registered higher mean values for HT women than for NT subjects. The mean values of the studied variables, except for height, differed significantly in the compared groups even after adjustment for age; and our results revealed that HT women have statistically significantly more fat mass (%) and less fat-free mass (%) than NT women (40.8% vs. 34.8%, $p < 0.001$ and 59.2% vs. 65.1%, $p < 0.001$, respectively).

Table 2 summarizes the distribution of participant lifestyle characteristics, obesity, and FTO genotype and highlights the following results; the frequency of smokers and the practice of regular exercise were almost the same in HT and NT women; the frequency of postmenopausal women was higher in the HT women's group (63.1%) compared to NT subjects (36.9%) and the frequency of university education was higher in the NT women (22.8%) than those with HT (16.5%; both p-values were < 0.001). Our results for HT women also show that 80.0% had BMI ≥ 25 kg/m2, 74.9% had higher than optimal WHR values at ≥ 0.81 and 85.1% had higher WHtR values ≥ 0.49. In contrast, the NT women had lower percentages of increased values for BMI index (47.5%), WHR index (43.6%), and WHtR index (52.4%). These differences were statistically significant at $p < 0.001$. The distribution of the three FTO rs17817449 genotypes fell within the Hardy-Weinberg equilibrium, and the HT and NT women's groups did not differ significantly in the three-genotype distribution ($\chi 2 = 0.371$, df = 2, $p = 0.831$).

Table 3 shows the effect of anthropometric and body composition parameters on HT when this was tested by stepwise discriminant analysis. The WHtR abdominal obesity index was selected as the best predictor of HT ($p < 0.001$) and also for differentiation between the compared groups of women. While other investigated variables were excluded by the discriminant stepwise statistics ($p > 0.05$), the high canonical coefficient reflected the large contribution of WHtR to the discrimination between groups (WHtR = 0.632, $p < 0.001$); and this was even higher than for age differentiation (age = 0.432, $p < 0.001$). Univariate analysis of covariance with age and WHtR as the covariates was used to test the effect of FTO gene

TABLE 1

BASELINE CHARACTERISTICS OF THE STUDY WOMEN

	Normotensive women			Hypertensive women				
Number of participants	n = 320			n = 255				
	Mean		SD	Mean		SD	p	p[a]
Age, years	47.4	±	5.3	52.4	±	6.1	<0.001	
Anthropometric characteristics								
Height, cm	163.7	±	5.7	163.0	±	6.0	0.145	0.892
Weight, kg	68.4	±	12.1	79.3	±	16.3	<0.001	<0.001
Waist circumference, cm	81.2	±	11.2	93.1	±	14.5	<0.001	<0.001
Hip circumference, cm	101.3	±	8.8	108.5	±	11.8	<0.001	<0.001
BMI, kg/m^2	25.1	±	4.3	29.5	±	6.1	<0.001	<0.001
WHR	0.8	±	0.1	0.9	±	0.1	<0.001	<0.001
WHtR	0.5	±	0.1	0.6	±	0.1	<0.001	<0.001
SBP, mmHg	119.6	±	14.3	134.7	±	15.7	<0.001	<0.001
DBP, mmHg	76.5	±	9.2	82.8	±	10.4	<0.001	<0.001
Body cell mass, %	47.2	±	2.1	47.6	±	3.6	0.694	0.559
Total body water, %	50.0	±	4.8	46.5	±	5.1	<0.001	<0.001
Extra cellular water, %	44.1	±	2.6	45.6	±	3.1	<0.001	<0.001
Intra cellular water, %	55.9	±	2.6	54.4	±	3.1	<0.001	<0.001
Fat mass, %	34.8	±	7.6	40.8	±	8.1	<0.001	<0.001
Fat free mass, %	65.1	±	7.6	59.2	±	8.1	<0.001	<0.001
Muscle mass, %	38.2	±	4.3	35.2	±	5.1	<0.001	<0.001
Basal metabolic rate,kcal	1398.1	±	107.3	1421.1	±	118.1	0.014	<0.001

Note: SD, standard deviation; p, value of statistical significance (comparison of means); pa-value of statistical significance adjusted for age (ANCOVA); BMI, body mass index; WHR, waist to hip ratio; WHtR, waist to height ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure

TABLE 2

DISTRIBUTION OF LIFE STYLE CHARACTERISTICS, OBESITY AND FTO GENOTYPE IN NORMOTENSIVE AND HYPERTENSIVE WOMEN

		Normotensive women		Hypertensive women		
		n	%	n	%	p
Smokers	No	222	69.4	179	70.2	0.832
	Yes	98	30.6	76	29.8	
Menopausal status	Premenopause	211	65.9	94	36.9	<0.001
	Postmenopause	109	34.1	161	63.1	
Education	Primary	24	7.5	52	20.4	<0.001
	Secondary	223	69.7	161	63.1	
	University	73	22.8	42	16.5	
Regular sport activity	No	227	89.0	281	87.8	0.654
	Yes	28	11.0	39	12.2	
BMI category	BMI < 24.99	168	52.5	51	20.0	<0.001
	BMI ≥ 25.00	152	47.5	204	80.0	
WHR category	WHR < 0.81	180	56.4	64	25.1	<0.001
	WHR ≥ 0.81	139	43.6	191	74.9	
WHtR category	WHtR < 0.49	152	47.6	138	14.9	<0.001
	WHtR ≥ 0.49	167	52.4	217	85.1	
FTO rs17817449	GG	60	22.7	50	20.6	0.831
	GT	140	53.0	131	53.9	
	TT	64	24.3	62	25.5	

Note: n, number of participants; BMI, body mass index; WHR, waist to hip ratio; WHtR, waist to height ratio; p, value of statistical significance

TABLE 3

THE EFFECT OF SELECTED ANTHROPOMETRIC/BODY COMPOSITION VARIABLES ON THE HYPERTENSION INCIDENCE

Dependent variable: Hypertension						
Independent variables	Tolerance	F to Remove	Wilks' Lambda	Standardized Canonical Discriminant Function Coefficients	Exact F	p
WHtR	0.951	72.763	0.840	0.632	129.673	<0.001
Age	0.951	53.708	0.815	0.432	97.665	<0.001

Note: All other investigated body composition and anthropometric parameters, with p-value > 0.05, were excluded from the analysis by discriminant stepwise method; WHtR, waist to height ratio; p, value of statistical significance

variant and MS on SBP and DBP in HT women (Table 4). The results in this table show that a significant association was recorded only between the studied gene variant and DBP (p = 0.044). Women possessing at least one risk allele (GG or GT) had slightly higher mean values of DBP than those without this allele (estimated marginal means, 83.8 ± 10.9 vs. 80.6 ± 8.2 mm/Hg, data not shown in table). In the next step, we analyzed the effect of FTO gene variant and MS on SBP and DBP in NT women (Table 5). Herein, univariate analysis of covariance highlights that the FTO gene variant did not have the sole effect on SBP (p = 0.881). This was evident after the adjustment for age and anthropometric continuous covariate with the strongest impact on blood pressure in our sample, WHtR. However, our results showed a statistically significant association between MS and the FTO genotype and their common effect on SBP with an observed power of 0.871 (p = 0.002). In addition, the pairwise comparison depicted in Figure 1 graphically illustrated the different effect of FTO gene variant in the late pre-, perimenopausal period and in the postmenopausal period. The pre-, perimenopausal G- allele carriers had lower SBP values in comparison with TT genotype carriers (estimated marginal means, 116.9 vs. 122.9 mm/Hg), while postmenopausal G- allele carriers had higher SBP values compared to TT genotype carriers (estimated marginal means, 120.7 vs. 114.1 mm/Hg). We did not notice any significant associations between FTO, menopause, and DBP.

TABLE 4

ASSOCIATION BETWEEN FTO GENE VARIANT, MENOPAUSAL STATUS AND BLOOD PRESSUREIN HYPERTENSIVE WOMEN

Predictors	F	p	Observed Power
Dependent variable: systolic blood pressure			
Age, y	1.123	0.290	0.184
WHtR index	2.164	0.143	0.311
Menopausal status	0.186	0.667	0.071
FTO (GG + GT vs. TT)	3.378	0.067	0.449
Menopausal status * *FTO* (GG + GT vs. TT)	2.646	0.105	0.367
$R^2 = 0.036$ (Adjusted $R^2 = 0.016$)			
Dependent variable: diastolic blood pressure			
Age, y	6.040	0.015	0.687
WHtR index	1.403	0.237	0.218
Menopausal status	1.207	0.273	0.194
FTO (GG + GT vs. TT)	4.111	0.044	0.524
Menopausal status * *FTO* (GG + GT vs. TT)	0.501	0.480	0.109
$R^2 = 0.053$ (Adjusted $R^2 = 0.033$)			

Note: WHtR, waist to height ratio; p, value of statistical significance; F, ratio of two variances

TABLE 5

ASSOCIATION BETWEEN FTO GENE VARIANT, MENOPAUSAL STATUS AND BLOOD PRESSURE IN NORMOTENSIVE WOMEN

Predictors	F	p	Observed Power
Dependent Variable: systolic blood pressure			
Age, y	3.581	0.060	0.470
WHtR index	10.716	0.001	0.903
Menopausal status	1.083	0.299	0.179
FTO (GG + GT vs. TT)	0.023	0.881	0.053
Menopausal status * *FTO* (GG + GT vs. TT)	9.635	0.002	0.871
$R^2 = 0.108$ (Adjusted $R^2 = 0.091$)			
Dependent Variable: diastolic blood pressure			
Age, y	1.018	0.314	0.171
WHtR index	10.198	0.002	0.889
Menopausal status	1.099	0.295	0.181
FTO (GG + GT vs. TT)	1.241	0.266	0.199
Menopausal status * *FTO* (GG + GT vs. TT)	2.889	0.090	0.395
$R^2 = 0.058$ (Adjusted $R^2 = 0.040$)			

Note: WHtR, waist to height ratio; p, value of statistical significance; F, ratio of two variances

Discussion and Conclusion

Our results of discriminant analysis indicate that the WHtR index seems to be a better predictor to screen women with HT compared to BMI and body composition parameters. These results correspond to a study published by Kazlauskaite et al.[39], where the WHtR index can be used for community-based screening of midlife women who need secondary prevention for cardiometabolic conditions. Similarly, in the study of Ge et al.[40] WHtR index is one of the best obesity indices and serves as an important predictor related to hypertension in young, middle-aged, and elderly women. We confirmed the effect of FTO gene variant on systolic blood pressure in Slovak NT women. Moreover, to the best of our knowledge, the data presented here is the first to indicate the important role of menopausal status in this investigated association. Many studies have examined FTO gene–blood pressure associations in various populations, but with inconsistent results and without including menopausal status in the analyses. For

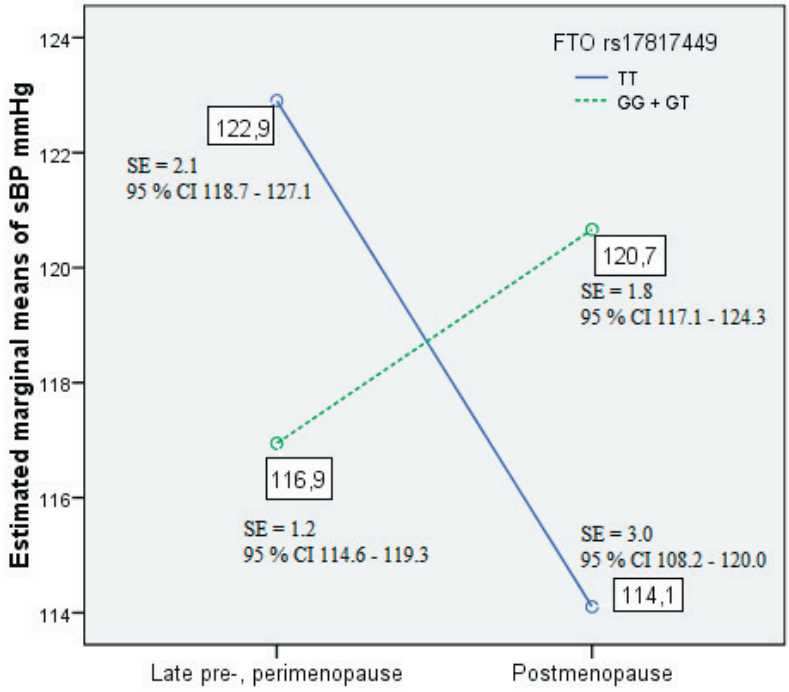

Fig. 1. The difference between late pre-, perimenopausal, and postmenopausal normotensive women in systolic blood pressure according to the FTO gene variant. Note: CI, confidence interval; SE, standard error of the estimated mean.

example, He et al.[18] stated in their meta-analysis that subgroup analysis based on ethnicity showed a significant association between FTO variant and hypertension in both European and Asian populations. However, the association remained significant only in Asians but not in Europeans on adjustment for BMI. Moreover, many association studies were focused on the investigation of different FTO single nucleotide polymorphisms (SNP's - rs8050136 and rs9939609)[32,41–43]. For example, the FTO polymorphism rs8057044 was associated with high blood pressure levels in the Tunisian population[44]. The mechanism underlying the association of the FTO variant with the risk of cardiovascular disease (CVD) remains unclear. It has been demonstrated that FTO protein is highly expressed in the hypothalamus which regulates energy homeostasis and metabolism, and the hypothalamus may therefore have an important role in the association of FTO and HT as a powerful blood pressure regulator[45–48]. Other studies have indicated that the FTO variant is associated with increased risk for HT through regulation of sympathetic modulation of vasomotor tone[32].

Notably, Hubacek et al.[26] believe that the FTO variant increases CVD risk through a further mechanism; by its likely effect on DNA methylation. Herein, the FTO gene variant interacts with unhealthy lifestyles, especially a high-fat diet and lack of physical activity, and this can therefore affect epigenetic status and ultimately contribute to the development of CVD[26]. Furthermore, many authors have associated FTO gene variants with obesity, BMI, hip circumference[17,39,49], visceral and subcutaneous fat mass[50] which are well-known CVD and HT risk factors[51–53]. Scuteri et al.[17] found that the rs17817449 G allele variant is strongly associated with obesity in European and Hispanic Americans. In addition, Villalobos-Comparán et al.[54] reported that FTO gene polymorphisms are a major risk factor for class III obesity in the Mexican population and that FTO gene expression is upregulated in the subcutaneous fat tissue of obese individuals. These associations have not been replicated in other ethnic groups including the Chinese[29], Japanese[30], and Oceanic[55] populations. Despite our interesting findings, we are aware that the interpretation of our results is confronted by some limitations. Firstly, the sample size of women was relatively small (n = 575) and for future studies, it would be paramount to enlarge the study sample for a detailed analysis. Further, only one FTO SNP was investigated in this study, so it is unclear whether the identified association is due to this specific variant or to another variant in tight linkage disequilibrium with rs17817449. We do not know also how many hypertensive participants are on prescribed HT treatment, and if so, for what length of time. Therefore, the values of blood pressure and also results from FTO – DBP association analysis in HT women, may have been influenced to some extent by the inclusion of HT women currently under antihypertensive treatment. Moreover, the relationship between antihypertensive

treatment, FTO gene variants and blood pressure in HT women is currently not known, we cannot exclude a bias in our result. Therefore, it is necessary to replicate and to confirm our result in further pharmacogenetic population studies. Finally, the study is cross-sectional and may have had selection bias during participation recruitment, and the particular study design may limit result generalization to all Slovak midlife women.

In conclusion, our findings indicate that FTO rs17817449 along with menopause are significant factors associated with systolic blood pressure in Slovak normotensive women.

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UČINAK VARIJANTE GENA FTO (RS17817449) I MENOPAUZE NA KRVNI TLAK U HIPERTENZIVNIH I NORMOTENZIVNIH ŽENA U SLOVAČKOJ

S A Ž E T A K

Ovo presječno istraživanje ispituje učinak masne mase i polimorfizma gena povezanog s pretilošću (FTO) i menopauze na krvni tlak u slovačkih žena srednjih godina. Pregledali smo ukupno 575 žena u dobi od 39 do 65 godina. Podaci su analizirani korištenjem univarijantne analize kovarijance kako bi se ispitao učinak rizične varijante gena FTO (alel G) i menopauzalnog statusa (MS) na krvni tlak u skupinama žena s hipertenzijom (HT) i normotenzijom (NT). Zabilježena je značajna povezanost između proučavane varijante gena FTO i dijastoličkog krvnog tlaka (DBP), ali samo u skupini HT žena ($p = 0,044$). Žene koje posjeduju barem jedan rizični alel (GG ili GT) imale su nešto više srednje vrijednosti DBP-a od onih bez tog alela. U sljedećem koraku, naši su rezultati pokazali statistički značajnu povezanost između MS-a i genotipa FTO i njihov zajednički učinak na sistolički krvni tlak (SBP) u skupini NT žena ($p = 0,002$). Nositeljice G-alela u kasnoj pre, perimenopauzi imale su niže vrijednosti SBP-a u usporedbi s nositeljicama genotipa TT (procijenjena granična vrijednost, 116,9 naspram 122,9 mm/Hg), dok su nositeljice G- alela u postmenopauzi imale više vrijednosti SBP-a u usporedbi s nositeljicama genotipa TT (procijenjena granična vrijednost, 120,7 naspram 114,1 mm/Hg). Nismo primijetili nikakvu značajnu povezanost između FTO, menopauze i DBP-a. Naši nalazi pokazuju da su FTO rs17817449 i menopauza značajni čimbenici povezani sa sistoličkim krvnim tlakom u slovačkih normotenzivnih žena.