

# *FTO gene-lifestyle interactions on serum adiponectin concentrations and central obesity in a Turkish population*

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1 ***FTO* gene-lifestyle interactions on serum adiponectin concentrations and**  
2 **central obesity in a Turkish population**

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42 ***FTO* gene-lifestyle interactions on serum adiponectin concentrations and**  
43 **central obesity in a Turkish population**

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45 The aim of the study was to investigate whether lifestyle factors modify the association fat  
46 mass and obesity-associated (*FTO*) gene single nucleotide polymorphisms (SNPs) and  
47 obesity in a Turkish population. The study included 400 unrelated individuals, aged 24-50  
48 years recruited in a hospital setting. Dietary intake and physical activity were assessed using  
49 24-hour dietary recall and self-report questionnaire, respectively. A genetic risk score (GRS)  
50 was developed using *FTO* SNPs, rs9939609 and rs10163409. Body mass index and fat mass  
51 index were significantly associated with *FTO* SNP rs9939609 (P=0.001 and P=0.002,  
52 respectively) and GRS (P=0.002 and P=0.003, respectively). The interactions between SNP  
53 rs9939609 and physical activity on adiponectin concentrations, and SNP rs10163409 and  
54 dietary protein intake on increased waist circumference were statistically significant  
55 ( $P_{\text{interaction}}=0.027$  and  $P_{\text{interaction}}=0.044$ , respectively). This study demonstrated that the  
56 association between *FTO* SNPs and central obesity might be modified by lifestyle factors in  
57 this Turkish population.

58 Keywords: *FTO* gene variant; obesity; gene-diet interaction; adiponectin; genetic risk  
59 score; physical activity

60

61 **Introduction**

62 Obesity has been recognised as a worldwide public health problem due to its rising  
63 prevalence and concomitant health problems. The prevalence of overweight and obesity in  
64 Turkey were reported as 64.4% and 28.8%, respectively by WHO (WHO, 2018). Obesity  
65 can lead to other chronic diseases including type 2 diabetes (T2D), cardiovascular diseases  
66 (CVD), hypertension, cancer and osteoarthritis (Forse et al. 2020). A combination of

67 interactions between genetic and environmental factors is required for the development of a  
68 complex disease such as obesity (Franks and McCarthy 2016; Milagro et al. 2020). Studies  
69 have identified approximately 140 genes to be associated with obesity, and the fat mass and  
70 obesity associated (*FTO*) gene has been reported to be the strongest susceptibility gene for  
71 human obesity (Pigeyre et al. 2016).

72 The *FTO* gene is located on chromosome 16q12.2 and codes for a protein with 2-  
73 oxoglutarate dependent nucleic acid demethylase activity which is involved in DNA repair  
74 and the accumulation of fat in the body (Clifton et al. 2006; Chen and Du 2019). *FTO* is  
75 highly expressed in the brain, including the hypothalamus, adipocytes, pancreatic islet cells,  
76 and adrenal glands (Frayling et al. 2007). *FTO* gene has been suggested to control energy  
77 homeostasis and food intake (Abete et al. 2020). Previous studies have shown that, of the  
78 various obesity susceptibility genes, single-nucleotide polymorphisms (SNPs) located in the  
79 first intron of *FTO* gene has provided the strongest evidence for genetic predisposition to  
80 obesity (Frayling et al. 2007; Scuteri et al. 2007; Speliotes et al. 2010; Loos and Yeo 2014;  
81 Babenko et al. 2019; Fonseca et al. 2020). The minor allele ‘A’ of the *FTO* SNP rs9939609  
82 has been consistently associated with higher BMI in various populations (Frayling et al. 2007;  
83 Hertel et al. 2011; Peng et al. 2011; Corella et al. 2012; Li et al. 2012; Qi et al. 2014; Wang  
84 et al., 2020; Schlauch et al. 2020). Furthermore, a meta-analysis reported that the association  
85 between the SNP rs9939609 and BMI was replicated in 13 cohorts with 38,759 participants,  
86 where individuals with the ‘AA’ genotype had 1.67-time higher odds of obesity than those  
87 with the ‘TT’ genotype (Frayling et al. 2007). In the Turkish population, the risk alleles of  
88 the *FTO* rs1421085 and rs9939609 polymorphisms were shown to have significant

89 associations with the risk of obesity in women and metabolic syndrome (MetS) in men  
90 (Guclu-Geyik et al. 2016).

91 Turkish adults are characterized with low levels of total and high-density lipoprotein  
92 cholesterol, and high risk of CVD, that distinguish them from Europeans (Onat 2001). They  
93 also have increased susceptibility to impaired glucose tolerance and MetS primarily driven  
94 by obesity (Onat and Can 2014). Among the non-communicable diseases (NCDs) that  
95 accounted for 88.0% of deaths in Turkey, CVD has shown to contribute to 47.73% of overall  
96 deaths (WHO, 2018). Targeting modifiable risk factors for NCDs including obesity could  
97 prevent many deaths. Therefore, several health promotion campaigns such as “Reducing  
98 Portion Sizes” and “Move for Health” have been implemented for the prevention of obesity  
99 in Turkey (WHO, 2016; OECD, 2017). However, obesity is a multifactorial disorder, and  
100 identifying gene-environment interactions are needed to understand the aetiology and  
101 pathophysiology of obesity and also to develop more effective personalised preventative  
102 strategies (Castillo et al. 2017; Dahlman and Ryden 2020). To date, several *FTO*-dietary  
103 intake interactions on obesity-related outcomes have been examined in different populations  
104 (Grau et al. 2009; Sonestedt et al. 2009; Lappalainen et al. 2012; Ortega-Azorin et al. 2012;  
105 Phillips et al. 2012; Vimalaswaran et al. 2012; Qi et al. 2014; Merritt et al. 2018; Saber-Ayad  
106 et al. 2019) however, there are no such studies to date in a Turkish population The  
107 investigations of the gene-diet interactions in different ethnic groups are crucial to develop  
108 personalised nutrition strategies for each ethnic group due to the genetic heterogeneity  
109 (Vimalaswaran 2017). The *FTO* SNP rs9939609 has been associated with several dietary  
110 components including dietary protein intake (Lappalainen et al. 2012; Qi et al. 2014; Merritt

111 et al. 2018) and the SNP rs10163409 in *FTO* was among the top associations in a large  
112 genome-wide meta-analysis study (GWAS) for total caloric intake (Chu et al. 2013).  
113 Therefore, this study aimed to assess whether *FTO* variants, rs9939609 and rs10163409, are  
114 associated with obesity in 400 Turkish individuals and to determine whether these SNPs  
115 interact with dietary intake and physical activity on obesity outcomes.

## 116 **Materials and Methods**

### 117 ***Study population***

118 A total of 400 unrelated individuals, aged 24-50 years, were recruited from the outpatient  
119 clinic of Department of Endocrinology and Metabolism at the Hacettepe University  
120 Hospitals, Ankara, Turkey. This study was conducted as part of the GeNuIne Collaboration  
121 that investigates the interactions between genetic and dietary factors on metabolic diseases  
122 in different ethnic groups (Vimalaswaran 2017). The study participants were screened based  
123 on the following inclusion criteria: 1) routine visits to the outpatient clinic, 2) aged 18-50  
124 years, and 3) having a BMI  $\geq 18.50$  kg/m<sup>2</sup>. The exclusion criteria were: 1) having specific  
125 health problems including, liver and kidney diseases, mental and psychological disorders,  
126 history of cancer, and serious endocrine disorders (hypothyroidism, hyperthyroidism or  
127 hypopituitarism), 2) history of bariatric surgery, 3) being pregnant or lactating, 4) using drugs  
128 that affect body weight. Researchers informed and invited the eligible participants for their  
129 participation in to the study. The study was approved by the local ethics committee of  
130 Hacettepe University (GO 15/612-11), and all the participants provided the signed written  
131 consent.

### 132 ***Study design***

133 A cross-sectional case-control study design was used, where participants were divided into  
134 two groups: obese (BMI  $\geq 25.00$  kg/m<sup>2</sup>, n=200) and non-obese (BMI= 18.50-24.99 kg/m<sup>2</sup>,  
135 n=200). All participants underwent a physical examination by the research endocrinologists,



136 followed by clinical, biochemical and lifestyle assessments, and genetic analysis of *FTO*  
137 SNPs rs9939609 and rs10163409.

### 138 *Anthropometrical Measurements*

139 Body weight and height were measured by standard methods using a calibrated digital scale  
140 (Seca 220 Scale, Germany). BMI calculation was based on the body weight (in kilograms)  
141 divided by the square of height (in meter) (WHO, 2020). BMI classification of the WHO was  
142 used to classify the individuals as non-obese ( $\text{BMI} < 25.00 \text{ kg/m}^2$ ) and obese ( $\text{BMI} \geq 25.00$   
143  $\text{kg/m}^2$ ) (WHO, 2005). The waist circumference (WC) was measured by a standard method  
144 (WHO, 2011). Increased WC (central obesity) was defined based on cut-points established  
145 for Turkish adults ( $\text{WC} \geq 90 \text{ cm}$  for men/  $\geq 80 \text{ cm}$  for women) (Sonmez et al. 2013). Body  
146 composition was analysed by bioelectrical impedance using the Tanita MC-980 MA Multi  
147 Frequency Segmental Body Composition Analyzer (USA). Fat mass index (FMI) was  
148 calculated based on the fat mass (in kilograms) divided by the square of height (in meter)  
149 (Peltz et al. 2010). All anthropometrical measurements were taken by the research dieticians.

### 150 *Biochemical and clinical measures*

151 Serum adiponectin was analysed by ELISA kits (Ebioscience, Austria) at Hacettepe  
152 University Hospitals, Clinical Pathology Laboratory. The physical examination included the  
153 measurement of systolic (SBP) and diastolic blood pressure (DBP) using a stethoscope and  
154 sphygmomanometer in the right arm of the participants after sitting in a comfortable position  
155 in a quiet room for at least 15 min. Both blood pressures were measured twice at 5-minute  
156 intervals and recorded on average (Frese et al. 2011).

157 ***Dietary assessment***

158 Dietary intake was assessed using 24-hour dietary recall method that was carried out by  
159 trained research dietitians. A photographic atlas of food portion sizes and common household  
160 measures were used to facilitate the quantification of the amount of food consumed. Total  
161 energy, macro- and micronutrient intakes of participants were analysed from the records  
162 using BeBIS software (BeBIS, Nutrition Information System, Version 8).

163 ***Other lifestyle factors***

164 The socio-demographic characteristics, family and medical history, smoking and alcohol  
165 consumption were recorded. The physical activity level was assessed using the Turkish  
166 version of the International Physical Activity Questionnaire (IPAQ) (Saglam et al. 2010).

167 ***SNPs selection and genotyping***

168 *FTO* gene was selected based on its consistent and strong associations with obesity traits in  
169 large-scale GWASs (Frayling et al. 2007). The SNP rs9939609 is the most commonly studied  
170 variant and consistently associated with obesity phenotypes across multiple ethnicities  
171 (Frayling et al. 2007; Hertel et al. 2011; Peng et al. 2011; Corella et al. 2012; Li et al. 2012;  
172 Loos and Yeo 2014; Qi et al. 2014) and SNP rs10163409 has been shown to be associated  
173 with dietary energy intake from macronutrients (Chu et al. 2013). Therefore, *FTO* SNPs,  
174 rs9939609 and rs10163409, which have been shown to be associated with obesity traits and  
175 dietary intake in large GWASs, were genotyped. The genotype frequencies of the *FTO* SNPs,  
176 rs9939609 and rs10163409, were in Hardy Weinberg equilibrium ( $p > 0.05$ ).

177 The genomic DNA was extracted from the whole blood in K2EDTA containing tubes  
178 by the salting out method. Genotyping of the SNPs, rs9939609 and rs10163409, were  
179 performed using KASP assay (a competitive allele-specific polymerase chain reaction that  
180 incorporates a fluorescent resonance energy transfer quencher cassette), and the KASP  
181 primers were designed using Kraken software system (LGC, <https://www.lgcgroup.com>).  
182 Genotyping assays were carried out according to the manufacturer's instructions with a 7500  
183 Real time PCR System (Applied Biosystems). The following thermal cycling profile were  
184 used: 15 min at 94°C; 10 cycles of 20 s at 94°C, 60 s at 61°C with decrement -0.6°C/per  
185 cycle and 26 cycles of 20 s at 94°C, 60 s at 55°C; 60 s at 37°C.

#### 186 *Statistical analysis*

187 SPSS software (version 23.0) was used for statistical analysis. The Hardy-Weinberg  
188 equilibrium was assessed using the  $\chi^2$  goodness-of-fit test. Genotype frequencies and  
189 distribution in groups were compared using Pearson's chi-squared test. Continuous variables  
190 are presented as means and standard deviations (SD), and groups were compared using the  
191 independent t-test.

192 As the number of individuals with rare homozygous genotypes was low, a dominant  
193 model was used, where common homozygous genotypes were compared to combined rare  
194 homozygous and heterozygous genotypes. A genetic risk score (GRS) was created from both  
195 the *FTO* SNPs where the presence of one risk allele of any of the variants was scored as one  
196 point. This GRS ranged from 0 (homozygous individuals for non-risk alleles) to 4 points  
197 (homozygous individuals for the risk alleles of both *FTO* polymorphisms). The GRS variable

198 was then categorised into two groups based on the number of points; 1st group: individuals  
199 with scores of <2 points; 2nd group: individuals with scores of  $\geq 2$  points.

200 The independent and joint effects of *FTO* SNPs on the risk of obesity were assessed  
201 using the odds ratios (ORs) and 95% confidence intervals (CIs) that were calculated by  
202 logistic regression models. Also, the associations between *FTO* polymorphisms (separately  
203 and joint) and the continuous outcomes were tested using general linear models. Models were  
204 adjusted for age, gender, hypertension, CVD and obesity status wherever appropriate.  
205 Furthermore, *FTO* gene-environment interactions on continuous and categorical outcomes  
206 were tested using linear and logistic regression models, respectively. Interactions were  
207 investigated by including the interaction terms (e.g., carbohydrate\*genotype) in the  
208 regression models. Environmental factors that were investigated included dietary intake  
209 (carbohydrate, protein, fibre and fat intakes in grams/day) and physical activity. Furthermore,  
210 statistically significant interactions were investigated in more depth, where individuals were  
211 stratified by the tertiles of the lifestyle factor.

## 212 **Results**

### 213 *Characteristics of the Participants*

214 Obese individuals were older, and had higher BMI, WC and FMI and lower adiponectin  
215 levels than the controls ( $P < 0.001$ , for each). The cases and controls were not statistically  
216 different in terms of their food intake and physical activity levels ( $P > 0.05$ ) (Table 1).

### 217 *Associations between *FTO* variants and obesity-related traits*

218 Genotype distributions and minor allele frequencies (MAFs) for both SNPs are shown in  
219 Table 2. The MAFs of the SNPs, rs10163409 and rs9939609, were T=0.37 and A=0.39,

220 respectively. The associations between SNP rs9939609 and BMI (P=0.001) and FMI  
221 (P=0.002) were found significant where the 'A' (AT/AA) allele carriers had significantly  
222 higher BMI and FMI than 'TT' homozygotes (Table 3). Furthermore, 'A' allele carriers had  
223 significantly higher WC (P=0.007) and lower adiponectin levels (P=0.031) compared to non-  
224 carriers. The *FTO* SNP rs10163409 did not show any significant association with obesity  
225 traits (Table 3).

### 226 *Interactions between FTO variants and dietary intake on obesity-related traits*

#### 227 *FTO gene-dietary protein intake interactions*

228 The significant interactions between SNP rs10163409 and protein intake on the risk of  
229 increased WC ( $P_{\text{interaction}}=0.044$ ) and WC as a continuous variable ( $P_{\text{interaction}}=0.007$ ) were  
230 observed. Stratification of the dietary protein intake into tertiles showed that, in the highest  
231 tertile group with a mean  $\pm$  SD of  $138\pm 38$  g/day protein intake, 'T' allele carriers of the SNP  
232 rs10163409 had a significantly higher risk of central obesity [OR= 3.3 (95% CI: 1.149-  
233 9.478), P=0.027] than those with 'AA' genotype (Figure 1).

#### 234 *Interactions between FTO variants and physical activity on obesity-related traits*

235 The interaction between the SNP rs9939609 and physical activity levels on adiponectin  
236 concentrations was statistically significant ( $P_{\text{interaction}}= 0.027$ ), where, among those with  
237 lowest levels of physical activity, the adiponectin concentrations were significantly lower in  
238 the allele 'A' carriers compared to individuals with 'TT' genotype (P=0.006) (Figure 2).

#### 239 *Associations between GRS and obesity-related traits*

240 The GRS was significantly associated with BMI (P=0.002), FMI (P=0.003) and increased  
241 WC (P=0.02) (Figures 3a, 3b and 3c). However, the interactions between GRS and lifestyle  
242 factors on obesity traits were not found statistically significant.

### 243 **Discussion**

244 To our knowledge, this is the first study that investigated the interaction between *FTO* SNPs  
245 and dietary intake on obesity traits in a Turkish population. This study has identified the

246 associations of the *FTO* SNP rs9939609 and GRS with obesity traits, and also showed that  
247 the physical activity level can modify the effect of the minor allele ‘A’ of the *FTO* SNP  
248 rs9939609 on adiponectin concentrations, a biomarker of metabolic syndrome (Stojanovic et  
249 al. 2015). Furthermore, our study has demonstrated that the higher protein intake was  
250 associated with higher risk of central obesity among the ‘T’ allele carriers of the *FTO* SNP  
251 rs10163409 compared to non-carriers. Since Turkish adults have a sedentary lifestyle (WHO,  
252 2018), our findings contribute to the development of effective public health strategies  
253 focusing on the prevention and management of central obesity and CVD in Turkish  
254 population (IHME, 2017).

255 This study has shown that the risk allele ‘A’ of the *FTO* SNP rs9939609 was significantly  
256 associated with higher BMI and FMI, in agreement with the findings from other populations  
257 (Frayling et al. 2007; Do et al. 2008; Hertel et al. 2011; Peng et al. 2011; Corella et al. 2012;  
258 Li et al. 2012; Muc et al. 2015; Merra et al. 2020). A meta-analysis performed on 177,330  
259 individuals from multiple ethnicities have demonstrated an association between *FTO*  
260 rs9939609 genotype and BMI, suggesting a higher BMI in ‘A’ allele carriers (effect per  
261 allele=0.30 [0.30, 0.35] kg/m<sup>2</sup>, P=3.6\*10<sup>-107</sup>) (Qi et al. 2014). The reported *FTO*-related  
262 genetic associations with BMI have also been confirmed in a study in the Turkish population  
263 (Guclu-Geyik et al. 2016), where the *FTO* risk allele, ‘C’, carriers of the SNP rs1421085,  
264 which is in a high linkage disequilibrium (LD) (D’=0.967, r<sup>2</sup>=0.85) with the SNP rs9939609,  
265 had significantly increased BMI. Furthermore, parallel to the findings of other studies  
266 (Vimaleswaran et al. 2012; De Luis et al. 2016; Saucedo et al. 2017), we have also found that  
267 the *FTO* SNP rs9939609 was significantly associated with higher WC and lower adiponectin  
268 concentrations. On the contrary, there were no significant association between SNP  
269 rs10163409 and obesity. This could be explained by the fact that the SNP rs10163409 is not  
270 in LD with other *FTO* variants that have shown significant associations with BMI (Chu et al.  
271 2013).

272 Our study has provided evidence for gene-diet interaction in the Turkish population. We  
273 have demonstrated that, among those in the highest tertile of dietary protein intake, the risk  
274 of increased WC/central obesity was higher for the minor allele, 'T', carriers of the *FTO* SNP  
275 rs10163409 compared to those with AA genotype. To date, this is the first study analysing  
276 gene-diet interactions of the SNP rs10163409, suggesting that high intake of dietary protein  
277 might negatively affect WC in genetically susceptible individuals. However, studies  
278 investigating other *FTO* SNPs (rs1558902 and rs9939609) have reported conflicting results  
279 (Zhang et al. 2012; de Luis et al. 2015; Merritt et al. 2018). It has been suggested that  
280 following a high protein diet can modulate the genetic effect of *FTO* variants on obesity traits  
281 (Zhang et al. 2012; de Luis et al. 2015; Merritt et al. 2018). According to a 2-year weight loss  
282 intervention program, carriers of the risk allele 'A' of the *FTO* rs1558902 had a greater  
283 weight loss compared to non-carriers when high protein diets were consumed, whereas a  
284 negative genetic effect was found in response to a low-protein intake (Huang et al. 2014).  
285 The potential mechanism of *FTO* variants - protein intake interaction is still unclear,  
286 however, the regulation of food intake and appetite could be influenced. It has been found  
287 that the risk allele 'A' of the SNP rs9939609 was significantly associated with a greater  
288 reduction in food cravings and appetite scores among individuals who consumed high-  
289 protein diet but not in those in the low-protein diet (Huang et al. 2014). Regarding the SNP  
290 rs9939609, there were no significant interactions between the *FTO* variants and any of the  
291 dietary components on obesity traits. In agreement with our findings, a study of 11,091 adults  
292 from five European countries have found no interactions between the rs9939609 variant and  
293 the dietary intake of carbohydrate, glycaemic index, protein or fat on BMI, WC, weight gain  
294 and risk of obesity (Vimaleswaran et al. 2012). Furthermore, a meta-analysis of 40  
295 population-based studies reported that the total energy or macronutrient intakes had no effect  
296 on the association between the SNP rs9939609 and BMI (Qi et al. 2014). In contrast to our  
297 finding, a few large-scale studies demonstrated significant interactions between dietary

298 macronutrient intakes and *FTO* variants in determining BMI (Grau et al. 2009; Sonestedt et  
299 al. 2009; Corella et al. 2011; Lappalainen et al. 2012; Ortega-Azorin et al. 2012; Phillips et  
300 al. 2012). A cross-sectional study conducted on 4,839 Swedish participants reported an  
301 association between the risk allele of the SNP rs9939609 and higher BMI only in individuals  
302 with high fat and low carbohydrate consumption (Sonestedt et al. 2009). A similar interaction  
303 between the rs9939609 variant and saturated fatty acids (SFA) intake has been detected in  
304 2,163 individuals from two independent populations of the United States, where individuals  
305 homozygous for the risk allele ‘AA’ had a higher BMI compared to other genotypes, only  
306 when the intake of SFA was high (Corella et al. 2011). Furthermore, the *FTO* SNP  
307 rs8050136, in LD with rs9939609, significantly interacted with carbohydrate intake on  
308 obesity risk among Asian Indian population (Vimalaswaran et al. 2016).

309       Regarding genetic interactions with physical activity, a previous study conducted among  
310 200 Turkish adults found that BMI was higher in homozygous risk allele ‘A’ carriers of the  
311 SNP rs9939609 than the homozygote the ‘T’ allele carriers among physically inactive  
312 individuals (Kirac et al. 2016). The same interaction but on a biochemical measure of obesity  
313 (i.e.: adiponectin level), rather than BMI, was replicated in our study using a larger sample  
314 size. We found that, among those with lowest levels of physical activity, the adiponectin  
315 concentrations were significantly lower in the carriers of the risk allele ‘A’ of the *FTO*  
316 rs9939609 than ‘TT’ homozygotes. Adiponectin is a hormone produced and secreted by  
317 adipose tissue and commonly known for its antihyperglycemic, anti-inflammatory,  
318 antiatherogenic, and cardioprotective effects (Richard et al. 2020; Esmaili et al. 2020; Lee  
319 and Shao 2014). Studies have reported a strong correlation between the dysregulation of  
320 adipokine production and the onset of several metabolic abnormalities including CVD and  
321 cancer (Avogaro and de Kreutzenberg 2005; De Pergola and Silvestris 2013; Xiang et al.  
322 2020). The positive correlation between adiponectin levels and physical activity has been  
323 demonstrated in several studies (St-Pierre et al. 2006; Jurimae et al. 2010; Sirico et al. 2018),



324 where higher levels of physical activity have been shown to reduce adiposity which decreases  
325 the production of insulin and leptin, and increases adiponectin production (Nurnazahiah et  
326 al. 2016). Indeed, it has been reported that serum concentrations of adiponectin are inversely  
327 related to BMI, visceral body fat and blood concentrations of glucose, insulin, and  
328 triglycerides (De Rosa et al. 2013; Frithioff-Bojsoe et al. 2020). An intervention study  
329 conducted in 400 obese women showed that a weight reduction program resulted in a  
330 significant increase in adiponectin levels (Mavri et al. 2011). Given that this is the first study  
331 to report an interaction between *FTO* variant and physical activity on adiponectin  
332 concentrations, the findings need to be replicated in a larger Turkish cohort.

333 The main strengths of this study include the use of a biochemical marker of obesity (i.e.,  
334 adiponectin) and a well-characterised population. Nevertheless, there are some limitations  
335 which include the small sample size and the use of self-reported measurements in the  
336 assessment of dietary intake and physical activity. However, this study has still confirmed  
337 the associations between *FTO* SNP rs9939609 and obesity traits which were also reported in  
338 previous studies (Frayling et al. 2007; Hertel et al. 2011; Peng et al. 2011; Corella et al. 2012;  
339 Li et al. 2012; Merra et al. 2020; Schlauch et al. 2020). Given that obesity is a multifactorial  
340 condition, several genetic factors and lifestyle behaviours provide a predisposition to obesity;  
341 even though we have focused on the two important lifestyle factors, diet and physical activity,  
342 only two genetic variants were examined. However, to date, the *FTO* gene has been shown  
343 to be the strongest susceptibility gene for common obesity (Frayling et al. 2007; Scuteri et  
344 al. 2007; Speliotes et al. 2010; Loos and Yeo 2014). Furthermore, the cross-sectional design  
345 of this study limits the proof of causality. Even though our analysis was adjusted for several  
346 confounders, we cannot rule out the residual confounding caused by unknown factors.  
347 Therefore, the observed interactions needed to be confirmed in further studies with larger  
348 sample sizes.

349 **Conclusion**

350 In summary, this study has confirmed the associations between the risk allele ‘A’ of the *FTO*  
351 rs9939609 and GRS, with obesity related traits including BMI and FMI in this Turkish  
352 population. Our study suggests that the impact of the *FTO* polymorphisms, rs10163409 and  
353 rs9939609, on obesity among Turkish adults might be affected by dietary protein intake and  
354 physical activity levels, respectively, suggesting that increased consumption of protein-rich  
355 foods and sedentary lifestyle could possibly increase the genetic risk of central obesity. Our  
356 results provide significant public health implications, given that the rising prevalence of  
357 central obesity is a major public health problem in Turkey (Pekcan et al. 2017; WHO, 2018).  
358 Further studies with large sample size and objective measures of environmental factors are  
359 required to provide a better understanding of how these variants interact with lifestyle factors  
360 to develop effective prevention and treatment strategies for obesity.

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## Figure Captions

**Figure 1. Interactions of the *FTO* rs10163409 with tertiles of protein intake (g) on increased WC.** WC, Waist Circumference. Black bars implicate the ‘T’ allele carriers (TA+TT). *FTO* SNP rs10163409 showed a significant interaction with protein intake (g) on the risk of increased WC ( $P_{\text{interaction}}= 0.044$ ). Among those in the highest tertile of protein intake (mean  $\pm$  SD: 138 $\pm$ 38 g/day), the minor ‘T’ allele carriers of the SNP rs10163409 had a significantly higher risk of increased WC [OR= 3.3 (95% CI: 1.149-9.478),  $p = 0.027$ ] than those carrying ‘AA’ genotype. \*Odds ratio adjusted for age, gender, hypertension, cardiovascular diseases, total energy intake and obesity status

**Figure 2. Interactions between *FTO* rs9939609 variant and physical activity on adiponectin levels.** White bars indicate carriers of ‘TT’ genotype. Black bars implicate the risk allele, ‘A’, carriers (AT+AA). The regression model was adjusted for age, gender hypertension, cardiovascular diseases and obesity status. There was a significant interaction between the *FTO* SNP rs9939609 and physical activity on adiponectin levels ( $P_{\text{interaction}}= 0.027$ ), where, among those with low physical activity levels, carriers of the ‘A’ allele had significantly lower adiponectin levels compared to those with ‘TT’ genotype ( $p=0.006$ ).

**Figure 3. Association between the genetic risk score of the *FTO* SNPs, rs9939609 and rs10163409s and anthropometric measures of obesity.**

BMI, Body Mass Index; FMI, Fat Mass Index; WC, Waist Circumference. White bars: means of individuals with genetic risk score (GRS) of <2 risk alleles. Black bars: means of individuals with GRS of  $\geq 2$  or more risk alleles. The GRS was significantly associated with BMI (3a), FMI (3b) and WC (3c). Figure 3a; carriers of  $\geq 2$  or more risk alleles of the *FTO* variants (rs9939609 and rs10163409) had higher BMI ( $P=0.002$ ) compared to individuals carrying <2 risk alleles. Figure 3b; carriers of  $\geq 2$  or more risk alleles of the *FTO* variants (rs9939609 and rs10163409) had higher FMI ( $P=0.003$ ) compared to individuals carrying <2 risk alleles. Figure 3c; carriers of  $\geq 2$  or more risk alleles of the *FTO* variants (rs9939609 and rs10163409) had higher WC ( $P=0.020$ ) compared to individuals carrying <2 risk alleles. P values were obtained from linear regression analysis and adjusted for age, gender, hypertension, cardiovascular diseases and obesity status.