

Original Article

***FTO* Genotype Interacts with Improvement in Aerobic Fitness on Body Weight Loss During Lifestyle Intervention**

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Key Words

FTO · Aerobic fitness · Body weight · Lifestyle intervention

Abstract

Objective: Not every participant responds with a comparable body weight loss to lifestyle intervention, despite the same compliance. Genetic factors may explain parts of this difference. Variation in fat mass and obesity-associated gene (*FTO*) is the strongest common genetic determinant of body weight. The aim of the present study was to evaluate the impact of *FTO* genotype differences in the link between improvement of fitness and reduction of body weight during a lifestyle intervention. **Methods:** We genotyped 292 healthy subjects for *FTO* rs8050136. Participants underwent a 9-month lifestyle intervention. Before and after intervention, aerobic fitness was tested by bicycle (VO₂max) and treadmill spiroergometry (individual anaerobic threshold (IAT), subgroup of N = 192). **Results:** Participants lost body weight (p < 0.0001) independent of *FTO* genotype (p = 0.5). There was a significant correlation between improvement in VO₂max and decrease in body weight (p < 0.0001). *FTO* genotype interacted with this relationship (p = 0.0042 for VO₂max, p = 0.0049 for IAT). When stratifying the cohort according to their improvement in VO₂max, *FTO* obesity-risk A-allele carriers in the higher quartiles of improvement in fitness lost significantly less body weight. **Conclusions:** Our data reveal that genetic variation in *FTO* impacts on body weight reduction during lifestyle intervention only in subjects with marked improvement in aerobic fitness.

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Introduction

Over the past decades an alarming increase in the prevalence of obesity has taken place worldwide. Several lifestyle intervention programs were designed to prevent type 2 diabetes. Programs like the Diabetes Prevention Program (DPP) [1], the Finnish Diabetes Prevention Study (DPS) [2], and the German Tübingen Lifestyle Intervention Program (TULIP) [3] conclusively showed that besides diabetes prevention body weight loss is also feasible. However, not all participants responded to lifestyle interventions uniformly. Despite similar compliance, the response, especially the reduction of body weight and body fat but also enhancements in glucose tolerance and cardiorespiratory fitness, markedly differed among participants [4, 5].

In this context, genetic background plays an important role possibly explaining these differences in success of lifestyle intervention. Variation in *FTO* (fat mass- and obesity-associated) is the strongest common genetic determinant of body weight in children [6] and adults identified so far [7, 8]. The contribution of *FTO* polymorphisms to the success of lifestyle intervention is still controversial [9–11].

FTO is widely expressed in human tissues, including adipose tissue, skeletal muscle, and brain [12]. The association with body weight seems to be mainly due to higher food intake, while energy expenditure was not associated with this polymorphism in studies in humans [7, 13–15]. Underlying mechanisms may originate in the brain, where *FTO* variation determines function in animals [7] and humans [16–18]. At the molecular level, recent studies of Smemo et al. [19] and Claussnitzer et al. [20] indicate that the obesity-risk variation in *FTO* associates with expressional regulation of distant homeobox genes *IRX3* and *IRX5*. By turn, this affects mitochondrial metabolism and might be causal for the obesity association.

In humans, two studies that addressed associations of *FTO* variants with weight loss induced by exercise reported contrary results: Mitchell et al. [21] reported that women who exercised above study-specific exercise recommendations for 6 months lost more weight when they carried the obesity-risk allele. By contrast, risk-allele carriers lost less weight during a 20-week training program in a study reported by Rankinen et al. [22]. The mechanisms underlying this difference are unclear; different training regimens may contribute. For example, a more intense training regimen was applied by Rankinen et al. [22]. Furthermore, not weight loss per se but the relationship between improvement in cardiorespiratory fitness and weight loss might be affected by variation in *FTO*. Notably, the studies of Mitchell et al. [21] and Rankinen et al. [22] did not address the interaction between improvement of fitness and *FTO* genotype on amount of weight loss. Another study of Huuskonen et al. [23] cross-sectionally addressed the interaction of aerobic fitness and *FTO* genotype on body weight: aerobic fitness did not modify the association of *FTO* variation with body weight. Since this hypothesis has not been addressed longitudinally, we now investigated possible genotype differences in the link between improvement in aerobic fitness and reduction in body weight during a lifestyle intervention.

Material and Methods

Participants

292 volunteers from TULIP [24] were studied before and after 9 months of intervention. This study aimed to prevent diabetes in high-risk subjects by lifestyle intervention. Informed written consent was obtained, and the local ethics committee approved the protocol.

Lifestyle Intervention

After baseline measurements, participants underwent 9 months of intensive lifestyle intervention. Participants were instructed to perform at least 3 h of moderate sports/week below their individual anaerobic

threshold (IAT). Heart rate monitors (Polar, Büttelbronn, Germany) were given to participants. Compliance was controlled by walking protocols. Besides increased physical activity, lifestyle intervention included one session of dietary counseling each month aiming at a body weight reduction of at least 5% [24].

Phenotyping

Anthropometric measurements and 75 g oral glucose tolerance test (oGTT) (as described in [3]) were performed before and after 9 months of lifestyle intervention. Total body fat mass was measured by bioelectrical impedance (BIA-101; RJL Systems, Detroit, MI, USA).

Individuals completed a standardized, self-administered and validated questionnaire to measure physical activity, and a habitual physical activity (HPA) score was calculated [5].

Individuals underwent a continuous, incremental exercise test to volitional exhaustion using a cycle ergometer (Ergometrics 800 S, Ergoline, Bitz, Germany). Oxygen consumption was measured using a spirometry system (MedGraphics System Breese; MedGraphics, St. Paul, MN, USA). $\dot{V}O_2\max$ is expressed as $\dot{V}O_2$ per kg lean body mass (ml/min/kg).

A subgroup (N = 192) exercised on a treadmill with simultaneous heart rate recording at 3 km/h for 3 min and 6 km/h thereafter. After 6 min, treadmill inclined by 2.5% every 3 min. Lactate was measured every 3 min from capillary blood. Lactate curve was generated and plotted versus intensity of exercise (Ergonizer, Freiburg i.Br., Germany) [24].

Genotyping

We selected rs8050136 as a tagging SNP for a linkage block in *FTO* that is known to be associated with obesity [13]. DNA was isolated (NucleoSpin, Macherey&Nagel, Düren, Germany), and genotyping was performed using TaqMan assay (Applied Biosystems, Forster City, CA, USA). Genotyping reaction was amplified (GeneAmp 7000; Applied Biosystems). Fluorescence was detected on an ABI PRISM 7000 sequence detector (Applied Biosystems). The genotyping success rate was 100%. These genotyping results were validated by bidirectional sequencing in 37 randomly selected subjects and both methods gave 100% identical results. Of the subjects, 31% were C/C homozygotes (N = 89), 17% were A/A homozygotes (N = 53), and 52% were C/A heterozygotes (N = 150). The SNP was in Hardy-Weinberg equilibrium ($p = 0.8$).

Statistical Analyses

Statistical comparison between normally distributed parameters was performed using paired t-test. For non-normally distributed parameters log transformation was used. We performed multivariate linear regression models adjusted for gender, age, and baseline BMI to test differences between genotypes. Unless otherwise stated, we analyzed genotype differences under a dominant inheritance model. Reported effect sizes were standardized betas. P values ≤ 0.05 were considered statistically significant. The statistical software package JMP 11 (SAS, Cary, NC, USA) was used.

Results

Subject characteristics before as well as after 9-month lifestyle intervention are summarized in table 1. A total number of 292 subjects with a mean age of 46 ± 1 years participated. During lifestyle intervention, BMI significantly decreased from 29.8 ± 0.3 kg/m² to 28.9 ± 0.3 kg/m² ($p < 0.0001$) and also other parameters such as body fat mass, fasting blood glucose and 2-hour blood glucose decreased significantly (supplementary table 1, available at <http://content.karger.com/ProdukteDB/produkte.asp?doi=444145>). $\dot{V}O_2\max$ and IAT increased significantly in line with increase in HPA score ($p < 0.0001$).

FTO genotypes did neither associate with loss of body weight or body fat nor with improvement of glycemia or aerobic fitness ($\dot{V}O_2\max$, IAT) after adjustment for gender, age and baseline measurements (all $p > 0.09$, table 1). This holds also true when using an additive instead of a dominant inheritance model (all $p > 0.3$, data not shown).

However, there was a significant association between change in $\dot{V}O_2\max$ and change in BMI ($p < 0.0001$, $\beta = -0.3448 \pm 0.0165$, adjusted for gender, age, and baseline BMI). Subjects

Table 1. Associations of *FTO* rs8050136 with changes in anthropometric and metabolic parameters^a

	<i>FTO</i> rs8050136 genotype				Interaction p (intervention x <i>FTO</i> genotype)
	Before lifestyle intervention		After 9-month lifestyle intervention		
	CC	XA	CC	XA	
N (f/m)	89 (51/38)		203 (127/76)		
Age, years	45±1		46±1		
Weight, kg	86.4±1.7	88.0±1.4	83.7±1.6	85.6±1.4	0.4
BMI, kg/m ²	29.4±0.5	29.9±0.4	28.5±0.5	29.1±0.4	0.4
Body fat content, %	32.4±0.9	32.8±0.6	30.7±1	31.8±0.6	0.1
Fasting blood glucose, mmol/l	5.2±0.1	5.5±0	5.2±0.1	5.2±0	0.9
2-hour blood glucose, mmol/l	6.7±0.2	7.0±0.1	6.6±0.2	6.7±0.1	1.0
HPA score	8.1±0.1	8.1±0.1	8.6±0.1	8.6±0.1	0.7
VO ₂ max, ml/min/kg	24.6±0.7	23.7±0.4	25.3±0.7	25.0±0.5	0.3
IAT, W*	69.9±4.7	68.8±3.9	88.0±5.4	84.4±3.9	0.9

^aData are given as mean ± SE. p-values from a multivariate linear regression model adjusting for gender, age and baseline measurements of the respective trait using a dominant inheritance model.

*Data available from 192 subjects (CC = 60, XA = 132)

with the strongest improvement in VO₂max had a larger decrease in BMI ($p = <0.0001$, $\beta = -0.3471 \pm 0.0166$, adjusted for gender, age, and baseline BMI). Comparable results were found for IAT ($p = 0.0057$, $\beta = -0.20617 \pm 0.0085$, adjusted for gender, age, and baseline BMI).

For further analysis, we divided the cohort in quartiles according to their improvement in VO₂max. The 1st quartile comprised of subjects that even had a deterioration of VO₂max. In these subjects, there was no significant change in BMI during lifestyle intervention ($p = 0.8$; fig. 1a). From the 2nd to the 4th quartile, the extend of BMI reduction increased consistently with the larges change in subjects in whom VO₂max increased most (fig. 1a).

In the overall cohort as well as in the subgroup exercised on the treadmill, the relationship between improvement in fitness and relative BMI loss significantly interacted with *FTO* genotype ($p_{\text{ANCOVA}} = 0.0042$, $\beta = -0.17219 \pm 0.01795$ for VO₂max and $p_{\text{ANCOVA}} = 0.0176$, $\beta = -0.18739 \pm 0.00902$ for IAT, models adjusted for gender, age, and baseline BMI). Comparable results were obtained when repeating the analyses using an additive inheritance model instead of a dominant ($p_{\text{ANCOVA}} = 0.0051$ for VO₂max and $p_{\text{ANCOVA}} = 0.09$ for IAT, models adjusted for gender, age, and baseline BMI). Furthermore, when we included fold change in caloric intake in our model, the interaction remained significant ($p = 0.0040$).

Analyzing absolute change in body weight as an outcome, a comparable interaction between *FTO* variation and improvement in fitness was detected ($p_{\text{ANCOVA}} = 0.0030$, $\beta = -0.17545 \pm 1.527524$ for VO₂max and $p_{\text{ANCOVA}} = 0.0156$, $\beta = -0.18694 \pm 0.772764$ for IAT, models adjusted for gender, age, and baseline body weight).

Change in BMI during lifestyle intervention was not significantly different between *FTO* genotypes in the two quartiles of subjects with the lesser VO₂max improvement during lifestyle intervention (all $p > 0.6$; fig. 1b, left two column pairs). In contrast, obesity risk allele carriers lost significantly less weight in the upper two quartiles ($p = 0.05$, $\beta = -0.234 \pm 0.006$ or $p = 0.0451$, $\beta = -0.240 \pm 0.006$; fig. 1b, right two column pairs), despite a comparable improvement in VO₂max between genotypes in all fitness groups (all $p > 0.2$).

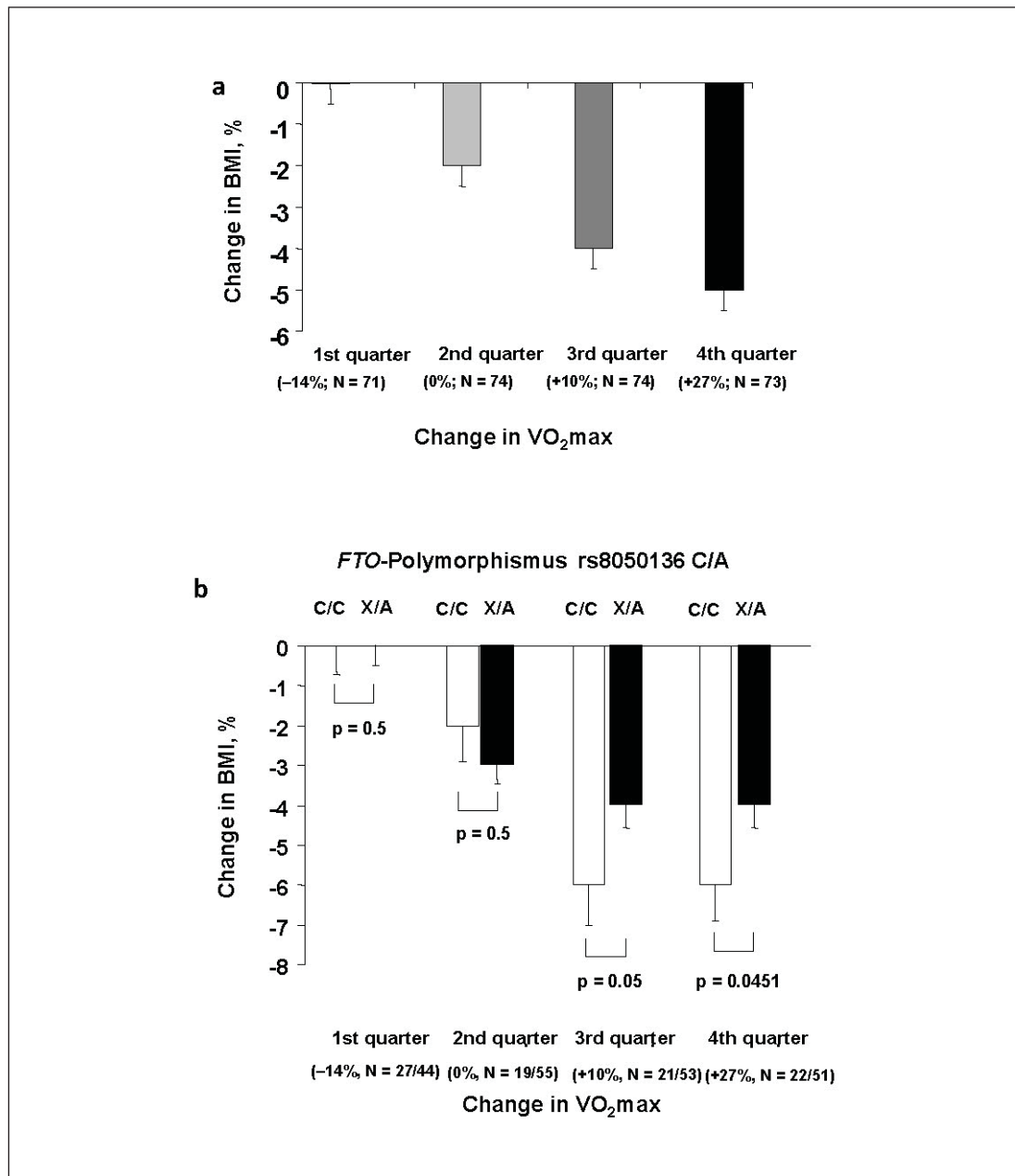


Fig. 1. a Interaction between changes in cardiorespiratory fitness and loss of body weight. Displayed are relative changes in BMI during 9 months of lifestyle intervention after stratification of participants according to their change in VO₂max. 1st quartile comprised of subjects that even had a deterioration of VO₂max. From the 2nd to the 4th quartile the extend of changes in VO₂max increased consistently. Change in BMI significantly differed between groups ($p < 0.0001$, adj. gender, age, BMI at baseline). Bars represent means \pm SEM. **b** *FTO* genotype determines the loss of body weight only in participants who strongly improved their cardiorespiratory fitness. The relationship between improvement in fitness and weight loss significantly interacted with *FTO* genotype ($p_{\text{ANCOVA}} = 0.0042$, adjusted for gender, age, and baseline BMI). Displayed are relative changes in BMI during 9 months of lifestyle intervention after stratification of participants according to their change in VO₂max. 1st quartile comprised of subjects that even had a deterioration of VO₂max. From the 2nd to the 4th quartile the extend of changes in VO₂max increased consistently. White bars are *FTO* non-risk allele carriers, while black bars are obesity risk allele carriers. Obesity risk allele carriers lost significantly less weight in the upper two quartiles. Genotype differences were tested in each group separately in multivariate linear regression models adjusted for gender, age and baseline BMI. Bars represent means \pm SE.

Discussion

During a 9-month lifestyle intervention program, participants lost more weight the more they improved their physical fitness. In the overall group weight loss was not statistically different between genotypes for the obesity risk variant in *FTO*. However, in those who improved their physical fitness most, weight loss was significantly smaller in carriers of the *FTO* obesity risk allele.

In line with Mitchell et al. [21], variation in *FTO* did not influence the improvement in fitness. Accordingly, in athletes performance was unaffected by *FTO* genotype [25]. In addition, *FTO* genotype was also not associated with amount of weight loss during lifestyle intervention, as shown before [10, 26].

We now hypothesized that *FTO* genotype interacts with the relationship between improvement in fitness and weight loss. Indeed, *FTO* genotype influenced the amount of weight loss only in participants with a strong enhancement in fitness. Within this group, obesity risk allele carriers lost significantly less weight. Such an interaction between genotype and exercise over time on weight loss has not been addressed in earlier studies [21, 22]. These two studies reported opposing results concerning the impact of *FTO* on weight loss during a lifestyle intervention. Differences between these studies with regard to training regimen or gender and correction for baseline body weight might explain the contradictory results. Our results might additionally explain part of the difference between these two previous studies: *FTO* genotype might have different or even opposite effects on weight loss depending on the amount of improvement of fitness.

FTO is expressed in human skeletal muscle. While expression levels are not different between genotypes [27], *FTO* variation associates with mitochondrial metabolism and energy efficiency in human skeletal muscle [28]. Furthermore, *FTO* variation influences a regulatory network that affects mitochondrial function [20]. Even if these results were obtained in adipocytes, comparable effects might be present in muscle as well. Therefore, differences in muscle metabolism between *FTO* genotypes could contribute to the interaction observed in our current study.

However, in humans the association between *FTO* variation and body weight seems to be mainly due to differences in food intake [14, 15]. Since our finding was statistically independent of food intake, we propose that other aspects besides food intake might contribute to obesity risk in humans as well.

However, especially in the subgroups our sample size is rather small compared to other genetic association studies. Furthermore, no independent cohort with comparable measurements was available for independent replication of our findings. We here focused on interactions with one specific polymorphism. Certainly a whole number of additional gene-gene or gene-lifestyle interactions are probable that are however beyond the scope of our current work.

While large cross-sectional studies suggested that *FTO* obesity risk allele carriers might benefit from exercise above average [29, 30], our interventional results and those from Rankinen et al. [22] indicate that this might not be the case. When improving fitness more than average in a lifestyle intervention program, *FTO* risk allele carriers might benefit less than average in terms of weight loss. As genetic background predisposes to obesity, it might under some circumstances also hamper weight loss through intensive exercise.

Authors Contributions

CS wrote the manuscript and performed metabolic tests (oGTT) and statistical analysis, VS and LF performed metabolic tests and contributed to discussion, TP performed bicycle and treadmill exercise test, FM performed genotyping, AN provided technical equipment for exercise testing and proof read the manu-

script, HUH initiated the TULIP study and proof read the manuscript, NS designed the exercise analysis and performed statistical analysis and proof read the manuscript, AF designed and performed the study and proof read the manuscript, MH wrote the manuscript and performed statistical analysis. All authors approved the final version of the manuscript before submission.

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Disclosure Statement

All authors have no conflicts of interest that are directly relevant to the content of this study.

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