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FTO Genotype and the Weight Loss Benefits of Moderate Intensity Exercise

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Abstract

The fat mass and obesity associated (*FTO*) gene was genotyped for the participants in the Dose-Response to Exercise in postmenopausal Women (DREW) trial and analyses were performed to determine if an *FTO* variant was associated with adiposity and cardiorespiratory fitness (CRF) before and after 6 months of moderate intensity exercise in Caucasian women (N=234). The A/A homozygotes for rs8050136 had a higher body mass index (BMI; kg/m^2) compared to C/C homozygotes at baseline (32.8 (0.6) vs. 31.0 (0.4) respectively; $p<0.05$) and at follow-up (31.9 (0.6) vs. 30.4 (0.5) respectively; $p<0.05$). Weight loss occurred post exercise, but there was no significant genotype by exercise interaction over time. Exploratory analyses among women exposed to moderate intensity exercise meeting, or exceeding, the physical activity recommendation found that those homozygous A/A lost significantly more weight than the C allele carriers (−3.3 (0.7) kg vs. −1.4 (0.4) kg and −1.5 (0.5) kg respectively; $p<0.05$). Cardiorespiratory fitness (CRF), defined as VO_{2peak} (oxygen consumption), increased post exercise and the magnitude of the increase was similar for each genotype. In conclusion, women genetically predisposed to being obese experienced weight loss and CRF benefits with moderate intensity exercise, with additional weight loss observed when the women met or exceeded the physical activity recommendations.

Introduction

The fat mass and obesity associated (*FTO*) gene (chromosome 16q12.2) has consistently been associated with measures of adiposity, especially among individuals of European Caucasian decent (1). The *FTO* gene is highly expressed in the hypothalamus, which is known to regulate energy homeostasis (2). There is accumulating evidence that *FTO* risk variants are associated with increased energy intake (3); whereas, in terms of energy expenditure, physical activity

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Disclosure

Dr Church reports having received honoraria for lectures from scientific, educational, and community groups; serving as a consultant for Trestle Tree Inc; and having a book in publication from which he will receive royalties. Dr Earnest reports having received honoraria for lectures from scientific, educational, and community groups. Dr. Blair serves on advisory boards for Jenny Craig, Technogym, and Alere; receives book royalties from Human Kinetics; and honoraria for lectures and consultations from scientific, educational, corporate, and community groups.

Trial Registration

clinicaltrials.gov Identifier: NCT00011193

seems to moderate the association between the *FTO* gene and obesity (4). Interestingly, a lifestyle intervention that predominantly advocated caloric restriction induced weight loss that was comparable across *FTO* genotypes (5).

The purpose of this study was to determine if an *FTO* variant was associated with obesity in a sample of Caucasian, postmenopausal, overweight and obese women. In addition, we also examined weight and cardiorespiratory fitness (CRF) changes after 6 months of moderate intensity exercise in relation to *FTO* genotype.

Subjects and Methods

The DREW trial is described in detail elsewhere (6). In brief, 464 eligible postmenopausal women (45–75 years old) were randomized to a non-exercise control group or to one of three exercise groups that provided 50%, 100% and 150% of the NIH Consensus Development Panel recommendations for physical activity (4, 8 or 12 kcal/kg/wk respectively) (7). Eligible participants had to be sedentary (≤20 minutes of exercise <3 days/week); have a BMI between 25.0–43.0 kg/m^2; have a systolic blood pressure between 120.0–159.9 mmHg; and be free from any serious medical condition. Ethical approval was granted by The Cooper Institute's institutional review board, and written informed consent was obtained from all participants.

Exercise Protocol, Body Composition and Insulin Sensitivity

The three exercise groups trained for 6 months, 3–4 sessions per week, at an intensity meeting 50% of the heart rate achieved at VO_{2peak}. All exercise sessions were closely supervised in an exercise training laboratory, with mean minutes per week spent on cycle ergometers or treadmill being 72.2 (12.3), 135.8 (19.5) and 191.7 (33.7) for the 50%, 100% and 150% exercise groups respectively. CRF (VO_{2peak}) was determined at baseline and at follow-up through cycle ergometry (Lode Excalibur Sport; Groningen, Netherlands), with oxygen consumption and carbon dioxide production measured every 15s (Parvomedics True Max 2400 Metabolic Measurement Cart); and heart rate was obtained from electrocardiograph measurements. Anthropometric measurements provided proxy measures of adiposity; the Homeostasis Model Assessment (HOMA) was used to provide a measure of insulin sensitivity; and pedometers (Accusplit Eagle, Japan) were used to document the steps accrued per day outside the supervised physical activity sessions.

Genotyping

Genotyping of the *FTO* rs8050136 SNP was conducted using the Illumina (San Diego, CA) GoldenGate chemistry and Sentrix Array Matrix technology on the BeadStation 500GX, using DNA extracted from leukocytes. For quality control purposes, five CEPH control DNA samples (NA10851, NA10854, NA10857, NA10860, NA10861; all samples included in the HapMap Caucasian panel) were genotyped in duplicate. Concordance between the replicates as well as with the rs8050136 genotypes from the HapMap database was 100%. Findings from the HapMap have previously shown that rs8050136 and rs9939609 are in very strong linkage disequilibrium (4).

Statistical Analysis

Only the Caucasian participants from the DREW trial, with complete weight measurements (n=234), were included in the present analyses, since rs8050136 has previously been shown to be associated with obesity predominantly in Caucasian populations (8). Linear mixed models (PROC MIXED), using unstructured covariance, were used to determine statistical significance with genotype by exercise interactions tested. All data are presented as least-square means with standard error (SE); statistical significance was set at an alpha level of 0.05 and all analyses were performed using SAS (version 9.2).

Results

At baseline and follow-up, A/A homozygotes had significantly higher weight and BMI compared to C/C homozygotes. Though post exercise weight loss occurred, no significant genotype by exercise interaction was found (Table 1). On account that the physical activity recommendation is the minimal volume recommended for health benefits, exploratory analyses restricted to the women who exercised at 100% and 150% of the recommendations revealed a significantly larger loss of weight after 6 months for A/A homozygotes compared to carriers of the C allele (Figure 1). The change in weight by rs8050136 genotype for all the participants and those exposed to the three exercise durations is shown in the Supplementary Figure 1.

Absolute and relative VO_{2peak} increased post exercise and this was consistent across genotypes. Values for HOMA tended to be higher among the A/A homozygotes compared to C allele carriers at baseline (Table 1) but the significant difference between A/A and C/C homozygotes was completely attenuated after adjusting for BMI (data not shown). There were no significant differences in the number of steps accrued per day outside the exercise training session (data not shown).

Discussion

Our findings support existing literature that has associated the *FTO* gene with adiposity. This is particularly significant considering that our sample was comprised of overweight and obese women. Regardless of genotype, the weight and BMI of the postmenopausal women were lower at follow-up compared to baseline, with comparable weight loss seen across *FTO* genotype. However, when exercising at, or above, the physical activity recommendations there was a significantly greater weight loss at 6 months among women who were A/A homozygotes for rs8050136.

In addition to weight loss, CRF increased in a dose-response manner to exercise volume. It is encouraging to note that a variant within the *FTO* gene did not inhibit the expected physiological increase in CRF seen with exercise, since the risk of all-cause mortality may be reduced with increased CRF, independent of adiposity (9). A finding that is even more pertinent considering that the *FTO* gene has been shown to increase the risk of early mortality independent of adiposity (10).

A lifestyle intervention promoting reduced caloric intake and increased physical activity found comparable weight loss across *FTO* genotypes at follow-up (5). Such a finding is supported by our results, in that genetically predisposed obese individuals are responsive to weight loss promoting exposures. However, our study focused only on the delivery of moderate intensity exercise in a controlled manner, whereas caloric restriction was the predominant focus of the lifestyle intervention described by Lappalainen *et al.* (5). While *FTO* risk variants have been associated with increased caloric intakes (3), treating obesity through reducing caloric intake alone would not additionally improve CRF.

Our sample consisted solely of overweight or obese Caucasian postmenopausal women and this should be considered when generalizing our findings to the wider population. With the small sample size, the power to detect statistically significant differences was reduced. Finally, it cannot be discounted that dietary changes contributed to our observations, but energy intake was not a focus of the DREW trial.

In conclusion, postmenopausal overweight and obese Caucasian women carrying two risk alleles for rs8050136 responded positively in terms of weight loss and CRF through moderate intensity exercise. The weight loss benefits were greater among the A/A homozygotes who were exposed to exercise that met, or exceeded, the physical activity recommendation.

Expending energy through moderate intensity exercise among postmenopausal women genetically predisposed to obesity is highly beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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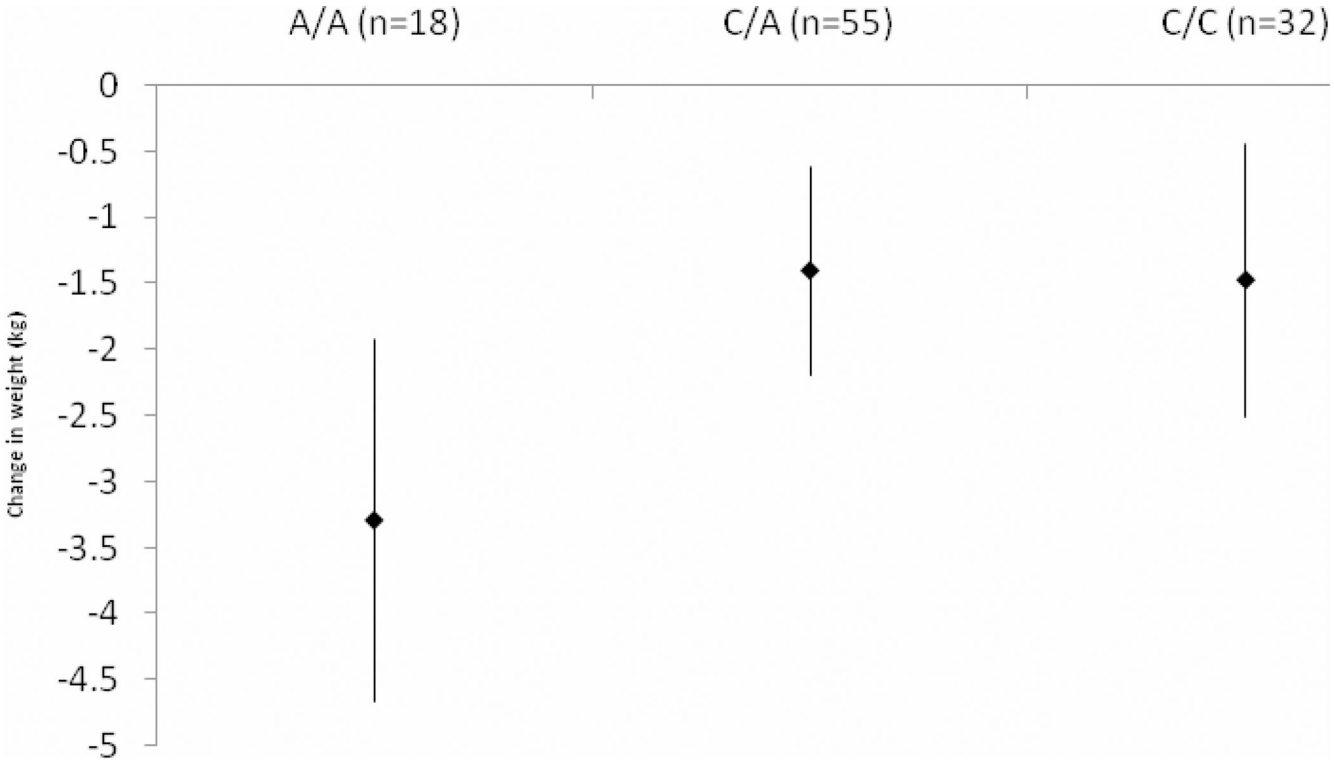

Figure 1.
change in weight from baseline to follow-up, by rs8050136 genotype, for women who exercised at 8 kcal/kg/week and 12 kcal/kg/week (n=105); adjusted for exercise group and baseline weight (A/A vs. C/A p=0.02 and A/A vs. C/C p=0.04)

Table 1

baseline and follow-up data, by genotype, concerning body composition and cardiorespiratory fitness

	***FTO* rs8050136**					
	Baseline			**6-month Follow-up**		
	A/A	**C/A**	**C/C**	**A/A**	**C/A**	**C/C**
	(n=38)	**(n=126)**	**(n=70)**	**(n=38)**	**(n=126)**	**(n=70)**
Age (years)	57.9 (6.0)	57.7 (6.6)	59.0 (5.7)			
Adherence (%)				99.5 (0.3)	99.6 (0.1)	99.6 (0.2)
Height (cm)	163.5 (0.9)	163.3 (0.5)	162.2 (0.7)	163.5 (0.9)	163.5 (0.5)	162.3 (0.7)
Weight (kg)	87.8 (1.9)	84.1 (1.0)	81.6 (1.4)[a]	85.3 (1.9)	82.8 (1.0)	80.2 (1.4)[b]
BMI (kg/m^2)	32.8 (0.6)	31.5 (0.3)	31.0 (0.4)[a]	31.9 (0.6)	30.9 (0.3)	30.4 (0.5)[b]
WC (cm)	103.6 (1.8)	102.3 (1.0)[c]	101.0 (1.4)	101.2 (1.8)	100.7 (1.0)	98.6 (1.4)[c]
HOMA	3.3 (0.3)	2.7 (0.2)[d]	2.5 (0.2)[a]	3.2 (0.3)[c]	2.6 (0.2)[c]	2.5 (0.2)
VO_{2peak} (L/min)	1.4 (0.04)	1.3 (0.02)	1.3 (0.03)[a]	1.4 (0.04)[c]	1.4 (0.02)	1.3 (0.03)[b]
VO_{2peak} (mL/min/kg)	15.8 (0.4)	15.9 (0.2)	15.5 (0.3)	17.1 (0.4)[c]	16.7 (0.2)	16.6 (0.3)

[a] differences at baseline compared to genotype A/A, adjusted for exercise assignment ($p<0.05$);

[b] differences at follow-up compared to genotype A/A, adjusted for exercise assignment ($P<0.05$);

[c] missing data (n=1);

[d] missing data (n=2)