The significance of the FTO gene on weight gain and body composition in young Swedish women with severe anorexia nervosa: a three-year follow-up study

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Abstract
Background: The aim of this prospective study was to investigate the potential influence of the fat mass and obesity-associated gene (FTO), SNP rs9939609, on body mass index (BMI) and body composition in women with severe anorexia nervosa during intensive nutrition therapy and after three years.
Methods: Twenty-five female anorexia nervosa patients (age 20.1±2.3 years, BMI 15.5±1.0 kg/m2) were treated for 12 weeks with a high-energy diet. FTO was genotyped and body composition parameters were assessed by dual-energy X-ray absorptiometry and peripheral quantitative computed tomography at baseline, after 12 weeks and at three-year follow-up.
Results: Patients gained, on average, 9.9 kg and BMI increased to 19.0±0.9 kg/m2 during intensive nutrition therapy. Fat mass increased, p<0.001, but total lean mass was stable. After three years, BMI remained stable, 19.4±3.3 kg/m2, as well as fat mass parameters and total lean mass. Muscle density decreased while the quotient fat/muscle area increased during nutrition therapy, but both then stabilized and remained stable after three years. There were no associations between FTO genotype and BMI or body composition parameters during the nutrition therapy or after three years. A tendency towards more stable BMI was observed in patients with the TT genotype and wider range in BMI for patients with the risk allele A after three years.
Conclusions: Irrespective of the FTO genotype, there was no difference in weight response during nutrition therapy, or at three-year follow-up. Hence, there is limited support for individualized therapy for anorexia nervosa based on FTO genotype.
Trial registration: Current Controlled Trials ISRCTN76310580. Date of registration: 15/01/2020. Retrospectively registered.

Background
The serious psychiatric illness anorexia nervosa (AN) is primarily found in teenage girls and young women. The condition is related to several long-term morbidities and mortality [1]. In the majority of cases, however, there is a gradual recovery from the disorder. In hospitalized AN patients intensive nutrition therapy, including an initial period of high caloric intake, has shown positive results [2].
Frayling et al. [3] identified an association between the fat mass and obesity-associated (FTO) gene, single nucleotide polymorphism (SNP) rs9939609, and increased body weight and body mass index (BMI). Homozygous carriers of the A allele (AA) had a higher body weight and a higher risk for obesity in comparison with persons homozygous for the T allele (TT). It seems to be involved in the regulation of hunger and satiety, and some studies indicate that FTO gene variants are associated with food intake [4–6]. Müller et al. [7] found an association between the A allele and both AN and bulimia nervosa (BN). In contrast, Jonassaint et al. [8] could not find any significant association with AN; however, their study pointed at other FTO SNPs than rs9939609. Celis-Morales et al. [9] demonstrated that physical activity attenuates the effect of FTO on BMI and waist circumference. West et al. [10] described that individuals with the A allele had higher physical activity levels than individuals with TT alleles despite similar adiposity-related measures.

Results from the 12-week intensive nutrition therapy are reported elsewhere but have not been studied in relation to the FTO genotype [2, 11]. We hypothesized that polymorphism of the FTO gene could explain the broad spectrum of individual weight gain during nutrition therapy and thereby provide a basis for individualized therapy. Furthermore, the FTO genotype may also influence the ability to maintain a normal BMI after initial nutrition therapy in patients with severe AN. This prospective study aimed to investigate the potential influence of the FTO gene on the development of BMI and body composition during intensive nutrition therapy and a three-year follow-up in Swedish young women with severe AN.

Methods
Study population and design
Participants included in this study were young women with severe AN admitted to the Queen Silvia Children’s Hospital, Gothenburg, Sweden from 2012 to 2014 for a planned intensive 12-week inpatient therapy with a structured behavioural program aimed at normalizing eating behaviour and restoring body weight. Inclusion criteria were age between 16 and 24 years and a diagnosis of AN according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [12]. The duration of AN (defined as the time since the diagnosis of AN first appeared in the patient’s record) was
median 44 months (minimum–maximum, 3-120 months) before inclusion in the study. At baseline, 18 (72%) patients had amenorrhea. Individuals with diabetes mellitus or inflammatory bowel disease were not included in the study. All eligible subjects and, if under 18 years their parents, were approached for assent and written informed consent. Two, out of twenty-seven eligible patients, declined to participate, giving 25 included patients. Three patients did not complete the inpatient therapy; for one patient the diagnosis of AN was reconsidered and the other two participants declined to complete the full 12-week therapy. Hence, 22 patients fulfilled the therapy. Patients underwent intensive nutritional rehabilitation for 12 weeks, with 24-h surveillance 7 days a week, as described by Pettersson et al. [2], with an extra-high-energy diet, starting at median 75 kcal/kg/day and step by step declining to 48 kcal/kg/day over the 12 week period. The nutrient intake was the recommended daily intake according to Nordic Nutrition Recommendations [13]. Patients were supervised by health care professionals 24 hours per day during the inpatient nutrition therapy period at the care anorexia ward, and they were not allowed to engage in physical activities. Body composition was assessed by dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) at baseline and after 12 weeks.

Three years after the 12-week inpatient treatment, 20 of the 22 patients participated in the follow-up study. Height, weight, DXA and pQCT were assessed, and patients answered a questionnaire regarding health and treatment for AN. This study was approved by the Regional Research Ethics Committee of Gothenburg, Sweden.

Genotyping
Genomic DNA was extracted from whole blood by the EZ1 BioRobot (Qiagen, Hilden, Germany) with the MagAttract DNA Blood Mini Kit (Qiagen). The FTO SNP rs9939609 (in intron 1 of FTO) was genotyped by polymerase chain reaction (PCR) and subsequent pyrosequencing. Each PCR reaction was run in 20 µL volume reactions on a Mastercycler® ep gradient S PCR cycler (Eppendorf AG, Hamburg, Germany), using the forward primer 5′-TCAAAACTGGCTCTTGAATGA-3′ and a biotinylated reverse primer 5′-TGCTCTCCACTCCATTTTTCT-3′ (Biomers.net, Ulm, Germany). Each PCR reaction contained 10 pmol of each primer, 1 × PCR buffer (Qiagen), 2 mM MgCl₂ (Qiagen), nuclease-free water
(Sigma, St. Louis, MO, USA), 0.2 mM deoxyribonucleoside triphosphate (ABgene, Epsom, UK) and 0.5 units Hot Star Taq® DNA Polymerase (Qiagen). The following PCR program was used: 94 °C 15 min, 45 × (94 °C 30 s, 53 °C 45 s, 72 °C 60 s), 72 °C 7 min, 4 °C. Pyrosequencing of the PCR products was performed using the PyroMark Q24 instrument (Qiagen) with the sequencing primer 5’-TGCGACTGCTGTGAATTT-3’ (Biomers.net) following standard procedures as reported elsewhere [14]. There are three available genotypes: AA, homozygous for the high-risk allele; TA, heterozygous; and TT, homozygous for the low-risk allele. The rs9939609 A allele is strongly associated with higher body weight and a higher risk for obesity compared with individuals lacking this risk allele [3].

Assessment of body composition
Body weight was measured with the same calibrated scale by a trained nurse and height was measured at admission and after three years. Fat mass and lean body mass were measured by DXA (Lunar Prodigy, GE Lunar Corp., Madison, WI, USA), n = 25 at start, n = 22 at 12 weeks and n = 10 at three years. At three years, 10 patients were measured with a newer Lunar iDXA (GE Lunar Corp.). In total, 20 healthy persons (age 6–37 years) were scanned twice by the same examiner in order to assess the in-vivo precision for Lunar Prodigy. The coefficients of variation (CV) for body fat mass and lean mass are reported elsewhere [15]. All DXA measurements were performed by the same nurse. A reliability study was performed with 25 individuals, comparing the Lunar Prodigy DXA with the Lunar iDXA for total fat mass and total lean mass. The reliability between the two methods was evaluated as acceptable, based on high intraclass correlation coefficient, > 0.98 for six parameters, and low CV, ranging between 1.3% and 3.3%, which has been reported elsewhere [16]. The Bland–Altman plots revealed no heteroscedasticity in data points.

For body composition we also used pQCT measurements on the left tibia at 4% and 66% of the tibia length using an XCT 2000 (Stratec Medizintechnik GmbH, Pforzheim, Germany) with software version 6.00. The performance of the device is reported elsewhere [11, 17].

Assessment of physical activity
The International Physical Activity Questionnaire (IPAQ) was developed in 1998 to facilitate surveillance of physical activity based on a global standard. The IPAQ (short form) records the
frequency and duration of activity per week, divided into four intensity levels, and was used to evaluate physical activity at the three-year follow-up [18]. Metabolic equivalent-minutes per week (MET-min/week) were calculated as duration × frequency per week × MET intensity (8.0 METs for vigorous-intensity activity, 4.0 METs for moderate physical activity, and 3.3 METs for walking). The total scores can then be categorized into three levels of physical activity: high: ≥ 3000 MET-min/week; moderate: 600–3000 MET-min/week; and low: < 600 MET-min/week.

Statistical analyses
Dichotomous variables were described by number and percentage and continuous variables by mean, standard deviation (SD), and median, minimum and maximum. The Wilcoxon signed rank test was used for tests of changes of continuous variables over time within a group. Associations between continuous variables and ordered categorical variables, e.g., FTO genotypes AA, TA and TT, were examined by first using the Jonckheere-Terpstra test as an overall test and then by using the Mann-Whitney U test for pairwise comparisons. Bland-Altman plots were used to assess the agreement and systematic difference between the Prodigy DXA and iDXA methods. Mixed model for repeated measures data, or more specifically covariance pattern models, was applied in order to analyse the longitudinal outcome measures over time for different FTO genotype groups. Visit, FTO genotype group and the interaction between the two were analysed as fixed effects, using Kenward-Roger degrees-of-freedom approximation, with visit as discrete repeated measures variable within patients using unstructured covariance pattern. All tests were two-tailed and conducted at the 0.05 significance level. All analyses were performed by using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA) or SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results
Intensive nutrition therapy, baseline to 12 weeks
At inclusion, the mean age of the subjects was 20.1 ± 2.3 years. Results for body composition parameters are presented in Table 1. The initial weight of the patients in this study was 44.0 ± 3.8 kg, which increased to 54.1 ± 3.7 kg at week 12 (p < 0.001). Individuals gained a median of 9.9 kg during the study period (23% of initial weight), and BMI increased from 15.5 ± 1.0 kg/m² to 19.0 ± 0.9 kg/m² (p < 0.001). During the intensive nutrition therapy, fat mass percentage, fat mass of the trunk and fat
mass of the left leg, measured by DXA, increased from baseline to 12 weeks (p < 0.001, Table 1).

Total lean mass was stable during the therapy period (Table 1).

Table 1
Body composition

|                          | Start (n = 25) | Week 12 (n = 22) | Three years (n = 20) | p-value start to week 12 | p-value week 12 to three years |
|--------------------------|---------------|------------------|----------------------|--------------------------|-------------------------------|
| Weight (kg)              | 44.0 ± 3.8    | 54.1 ± 3.7       | 55.2 ± 10.3          | < 0.001                  | 0.87                          |
| (36.6; 50.6)             | (44.0; 61.4)  | (39.0; 77.8)     |                      |                          |                               |
| BMI (kg/m²)              | 15.5 ± 1.0    | 19.0 ± 0.9       | 19.4 ± 3.3           | < 0.001                  | 1.00                          |
| (13.4; 17.3)             | (16.2; 20.6)  | (15.2; 28.0)     |                      |                          |                               |

DXA

|                          | Start (n = 25) | Week 12 (n = 22) | Three years (n = 20) | p-value start to week 12 | p-value week 12 to three years |
|--------------------------|---------------|------------------|----------------------|--------------------------|-------------------------------|
| Total fat mass (%)       | 14.0 ± 7.4    | 26.3 ± 5.8       | 24.8 ± 7.7           | < 0.001                  | 0.40                          |
| (4.4; 36.4)              | (16.9; 39.8)  | (8.7; 40.6)      |                      |                          |                               |
| Total fat mass (g)       | 6187 ± 3480   | 13796 ± 3451     | 13583 ± 6146         | < 0.001                  | 0.79                          |
| (1917; 17 061)           | (8604; 21 990)| (3786; 27 266)   |                      |                          |                               |
| Total lean mass (g)      | 37 526 ± 4139 | 38 586 ± 3758    | 39 440 ± 5247        | 0.43                     | 0.35                          |
| (29 864; 45 624)         | (32 226; 49 640)| (29 149; 47 575) |                      |                          |                               |
| Trunk fat mass (%)       | 11.5 ± 7.3    | 25.6 ± 5.8       | 21.7 ± 9.7           | 0.001                    | 0.06                          |
| (4.0; 36.9)              | (14.7; 40.7)  | (5.4; 42.7)      |                      |                          |                               |
| Trunk fat mass (g)       | 2522 ± 1719   | 6695 ± 1743      | 5756 ± 3370          | 0.001                    | 0.14                          |
| (821; 8746)              | (3627; 11 770)| (1244; 13 337)   |                      |                          |                               |
| Trunk lean mass (g)      | 19 284 ± 2243 | 19 363 ± 1893    | 19 679 ± 2447        | 0.11                     | 0.53                          |
| (14 958; 24 497)         | (15 716; 22 475)| (14 028; 22 555) |                      |                          |                               |
| Left leg fat mass (%)    | 17.5 ± 8.3    | 28.1 ± 6.6       | 28.8 ± 6.7           | 0.001                    | 0.46                          |
| (4.8; 37.5)              | (18.7; 39.4)  | (10.8; 40.9)     |                      |                          |                               |
| Left leg fat mass (g)    | 1286 ± 684    | 2451 ± 697       | 2713 ± 1076          | 0.001                    | 0.31                          |
| (319; 2976)              | (1437; 3918)  | (729; 5155)      |                      |                          |                               |
| Left lean leg mass (g)   | 5879 ± 701    | 6218 ± 846       | 6464 ± 1197          | 0.07                     | 0.30                          |
| (4690; 7428)             | (4738; 8343)  | (4880; 9111)     |                      |                          |                               |
| pQCT                     |               |                  |                      |                          |                               |
| Left leg muscle density (mg/cm²) | 79.3 ± 2.0 | 78.3 ± 1.4 | 78.0 ± 1.2 | 0.01 | 0.21 |
| (71.8; 81.5)             | (75.7; 81.4)  | (76.3; 79.8)     |                      |                          |                               |
| Left leg muscle area (mm²) | 5395 ± 785 | 5851 ± 752 | 6000 ± 993 | 0.002 | 0.24 |
| (3645; 6698)             | (4462; 7129)  | (4265; 7658)     |                      |                          |                               |
| Left leg fat/muscle area (%) | 27.7 ± 12.3 | 31.7 ± 13.1 | 33.0 ± 13.5 | 0.001 | 0.69 |
| (4.9; 44.7)              | (8.8; 53.9)   | (6.1; 55.2)      |                      |                          |                               |

Values are given as mean ± SD (minimum; maximum). For comparisons over time, the Wilcoxon signed rank test was used for continuous variables.

The distribution of the different FTO genotypes were: AA, n = 6 (24%); TA, n = 12 (48%); TT, n = 7 (28%). The observed genotype frequency was in accordance with the Hardy-Weinberg equilibrium (Chi-value = 0.85) using a significance level at 0.05. BMI increased significantly in all three groups during the intensive nutrition therapy (p < 0.001), however we could not demonstrate any difference in the change in BMI between patients with the three different genotypes when the additive, dominant, and recessive models of inheritance were applied (Fig. 1 and Table 2).
Table 2
Clinical data for FTO genotypes

|                      | Start | 12 weeks | Three years |
|----------------------|-------|----------|-------------|
|                      | AA (n = 6) | TA (n = 12) | TT (n = 7)   | AA (n = 5) | TA (n = 11) | TT (n = 6)   | AA (n = 5) | TA (n = 11) | TT (n = 4)   |
| Weight (kg)          | 44.9 ± 2.8 (40.0; 48.1) | 44.5 ± 4.1 (37.4; 50.6) | 42.2 ± 3.9 (36.6; 48.3) | 55.6 ± 2.2 (52.4; 57.6) | 54.1 ± 3.7 (47.8; 61.4) | 52.8 ± 4.8 (44.0; 57.7) | 58.3 ± 12.7 (43.0; 77.8) | 55.2 ± 10.9 (39.0; 76.2) | 51.6 ± 4.7 (45.8; 55.9) |
| BMI (kg/m²)          | 15.6 ± 0.5 (15.0; 16.3) | 15.7 ± 1.0 (14.5; 17.3) | 15.2 ± 1.3 (13.4; 20.1) | 18.9 ± 0.9 (16.2; 19.5) | 19.0 ± 0.4 (16.2; 20.6) | 19.0 ± 1.5 (15.2; 26.3) | 19.8 ± 4.0 (15.2; 28.0) | 19.5 ± 3.7 (15.2; 28.0) | 18.7 ± 1.6 (16.8; 20.3) |
| Total fat mass (%)   | 13.4 ± 7.5 (5.4; 23.2) | 14.8 ± 9.2 (4.4; 36.4) | 13.1 ± 3.6 (7.9; 19.4) | 24.0 ± 5.9 (16.9; 32.8) | 26.3 ± 6.8 (17.5; 39.8) | 28.1 ± 3.3 (23.7; 32.7) | 25.2 ± 4.0 (20.7; 31.7) | 25.1 ± 9.8 (16.0; 40.6) | 23.6 ± 5.5 (16.0; 29.0) |
| Trunk fat mass (%)   | 11.3 ± 6.9 (4.7; 22.2) | 12.1 ± 9.4 (4.0; 36.9) | 10.5 ± 2.3 (7.3; 14.0) | 23.6 ± 6.1 (14.7; 31.6) | 25.7 ± 7.0 (17.7; 40.7) | 27.1 ± 2.5 (23.5; 29.9) | 22.4 ± 6.3 (16.7; 33.0) | 21.9 ± 12.1 (10.4; 42.7) | 20.3 ± 7.0 (10.4; 26.0) |
| Left leg fat mass (%)| 16.7 ± 8.8 (6.4; 27.1) | 18.2 ± 9.8 (4.8; 37.5) | 17.1 ± 5.7 (9.6; 25.5) | 25.9 ± 7.2 (20.4; 37.0) | 27.8 ± 7.0 (18.7; 39.4) | 30.7 ± 5.3 (22.3; 36.9) | 28.8 ± 2.4 (25.8; 31.6) | 29.1 ± 8.6 (10.8; 40.9) | 27.8 ± 5.5 (22.6; 33.9) |

Values are given as mean ± SD (minimum; maximum). No significant differences between the FTO genotype groups were observed for these parameters, using mixed model for repeated measures data, when the additive, dominant, and recessive models of inheritance were applied.

Follow-up after three years
Twenty patients were followed for three years and their mean age was 23.6 ± 2.5 years. Mean weight was 55.2 ± 10.3 kg and BMI was 19.4 ± 3.3 kg/m², which was not significantly different in comparison with the weight and BMI measurements after 12 weeks. Seven patients (35%) were amenorrheic after three years.

Eighteen individuals (90%) received further treatment for AN after the intensive nutrition therapy period of 12 weeks. At the three-year follow-up, eight individuals (40%) still had ongoing treatment for AN, and in these patients all three FTO genotypes were represented (AA, n = 1; TA, n = 5; TT, n = 2). Two patients had no treatment during the 3-year follow-up period. Eighteen patients had one or several treatment sessions for AN during the follow-up period, 17 as outpatients, 9 as day care patients, and 7 as inpatients. After three years, six individuals (30%) rated their quality of life as good and four of these (20%) considered themselves being fully recovered from AN.

Total fat mass measured by DXA was stable from 12 weeks to three years, 24.8 ± 7.7% (p = 0.40). There was a trend towards decreasing trunk fat mass, from 25.6 ± 5.8% at discharge to 21.7 ± 9.7% after three years (p = 0.06). The corresponding values for left leg fat mass, total lean mass (measured by DXA), left leg muscle density, left leg muscle area and the left leg quotient of fat divided by muscle...
area (measured by pQCT) remained stable (Table 1).

BMI was stable in the three FTO genotype groups (AA, TA and TT) from 12 weeks to three years (Fig. 1). The change in total, trunk, and left leg fat mass did not differ significantly between the three FTO genotype groups. However, there was a tendency towards more stable BMI in patients with TT alleles and a wider range in BMI values for patients with AA and TA alleles after three years. Three patients presented a more pronounced increase in BMI (mean 19.2 to 26.4 kg/m²) and it is noteworthy that all these patients had the A allele.

The total physical activity was mean 3826 ± 3640 MET-min/week, median 2790 MET-min/week (198-15786). The level of physical activity was high in 10 individuals (50%), moderate in nine individuals (45%) and low in one individual (5%). The total level of physical activity was significantly higher in the TT group in comparison with the TA group, \( p = 0.04 \), but no difference was observed when comparing the TT group with the AA group. In addition, the amount of high physical activity was increased in the TT group in comparison with both the AA and the TA groups (\( p = 0.013 \)).

**Discussion**

This prospective interventional study, investigating the potential influence of the FTO gene on BMI and body composition in women with severe AN, could not demonstrate any impact of the FTO gene on weight gain during therapy with a strictly controlled high-energy diet. During the 12-week nutrition therapy with 24-hour surveillance, fat mass increased and muscle density decreased demonstrating that the BMI increase was mainly due to increased fat mass and not muscle mass. After three years of self-controlled energy intake, the range in BMI was greater but the FTO genotypes did not correlate to any of the measured weight or body composition parameters. From 12 weeks to three years, BMI and body composition parameters were stable and not related to FTO genotype.

Previous studies have revealed that carriers of the A allele present a significantly higher BMI and adiposity, as well as consuming a higher percentage of energy from fat [19, 20]. An association between the rs9939609 A allele and impaired satiety responsiveness and thus a direct effect on appetite has also previously been described [21]. An association between the FTO gene and both bulimia nervosa and AN has been demonstrated elsewhere [7]. Castellini et al. [22] found that the A
allele of the FTO rs9939609 was associated with a higher vulnerability to eating disorders, with the AA or AT genotypes present in 73% of patients with eating disorders but only in 53% of controls. They also found that the presence of the A allele was associated with binge eating behaviour and emotional eating, and they concluded that the A allele seems to represent a potential additive risk factor for persons with eating disorders to develop emotional eating and binge eating behaviours [22]. Similarly, we found a prevalence of 72% for either AA or AT in our material. Cecil et al. [23] observed that children with the A allele have a preference for energy-dense food. In contrast, Labayen et al. [24] showed that the FTO rs9939609 was not significantly associated with energy intake, but rather with the effect of the A allele on adiposity, which increased proportionally to the dietary fat content. Hakanen et al. [25] demonstrated no association between FTO genotype and energy intake or physical activity. However, West et al. [10] reported that individuals with the A allele reported higher total and vigorous physical activity levels compared with TT individuals. In contrast, at the three-year follow-up, we found that TT individuals reported a higher vigorous physical activity level than both AA and TA individuals, and a higher total physical activity level than the TA individuals. The strengths of this study are its prospective design, the long follow-up time, the small number of drop-outs and the use of the pQCT method, which contributes to the reliability of body composition data. The small number of included patients in the study may be considered as a major limitation; however, every participant underwent this 12-week nutrition therapy (with 24-h surveillance). This treatment is very staff-intensive and inclusion of a larger number of patients was not possible in our setting. In addition, the local anorexia ward changed the treatment protocol after 2014 to a more personalized treatment regime. After the 12-week hospitalized treatment period, each patient was handled individually. Different treatment regimens were used for a more personalized approach in patient care in this clinical setting. Further details concerning psychological, pharmacological and nutritional interventions are, unfortunately, not available for this study group due to relocation between different healthcare providers. The lack of a control group is another limitation that should be recognized. A control group was not included because we found it unethical to recruit normal-weight young women that would agree to a restricted diet with the objective of gaining fat mass and
weight in a hospitalized environment (with 24 h surveillance) for 12 weeks.

Conclusion

The hypothesis that the FTO genotype could affect the accumulation of fat and be a predictive factor for increased weight during intensive nutrition therapy in hospitalized patients with AN could not be verified. Nor could we demonstrate an association between the FTO genotype and the ability to maintain normal body weight after nutrition therapy. A tendency towards more stable BMI was observed in patients with the TT genotype and wider range in BMI for patients with the risk allele A after three years. Irrespective of the FTO genotype, there was no difference in weight response during nutrition therapy, or at three-year follow-up. Hence, there is limited support for individualized therapy for AN based on FTO genotype according to findings in the current study.

Declarations

**Ethics approval and consent to participate**

The study was approved by the Regional Research Ethics Committee of Gothenburg, Sweden. All eligible subjects, and if under 18 years their parents, were approached for assent and written informed consent prior to their inclusion in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study adheres to CONSORT guidelines.

**Consent for publication**

All eligible subjects, and if under 18 years their parents, were approached for assent and written informed consent for publication prior to their inclusion in the study.

**Availability of data and materials**

The datasets generated and analysed during the current study are not publicly available due to confidentiality under Swedish law but are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.
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**Authors’ contributions**

PM and DSE designed the study, advised on the data analysis and interpretation of results, and reviewed and revised the manuscript. AS and BT carried out the study design and data collection. AS performed the analysis and drafted the manuscript. AE contributed in interpretation of results and reviewed and revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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**Abbreviations**

SNP: single nucleotide polymorphism  
BMI: body mass index  
AN: anorexia nervosa  
BN: bulimia nervosa  
DXA: dual-energy X-ray absorptiometry  
pQCT: peripheral quantitative computed tomography
PCR: polymerase chain reaction

CV: coefficient of variation

IPAQ: international physical activity questionnaire

MET-min/week: metabolic equivalent-minutes per week

SD: standard deviation

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Figures

![Figure 1](image)

**Figure 1**

Individual BMI scores at start, week 12 and three years, categorized by FTO genotype. The solid horizontal line represents the mean BMI value and the dashed line represents the median BMI value for each FTO genotype. AA= homozygous for the high-risk allele A TA= heterozygous TT= homozygous for the low-risk allele T W1 = week 1 (start of nutrition therapy) W2 = week 12 (end of nutrition therapy) Y3 = Three-year follow-up

**Supplementary Files**

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