Fat and carbohydrate intake modify the association between genetic variation in the *FTO* genotype and obesity[1–3]

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ABSTRACT

Background: The fat mass and obesity–associated gene (*FTO*) has been shown to be associated with obesity and to influence appetite regulation.

Objective: The aim was to examine whether dietary factors (macronutrient and fiber intakes) and leisure-time physical activity modify the association between genetic variation in *FTO* and body mass index (BMI; in kg/m^2).

Design: A cross-sectional study examined 4839 subjects in the population-based Malmö Diet and Cancer study with dietary data (from a modified diet history method) and information on the genetic variant *FTO* (rs9939609). Direct anthropometric measures were made, and leisure-time physical activity was determined from the duration participants spent on 18 different physical activities.

Results: Significant interactions between energy-adjusted fat intake and *FTO* genotype ($P = 0.04$) and between carbohydrate intake and *FTO* genotype ($P = 0.001$) on BMI were observed. The observed increase in BMI across *FTO* genotypes was restricted to those who reported a high-fat diet, with a mean BMI of 25.3 (95% CI: 24.9, 25.6) among *TT* carriers and of 26.3 (95% CI: 25.8, 26.8) among *AA* carriers ($P = 0.0001$). The *FTO* variant was not associated with a higher BMI among subjects with lower fat intakes (BMI = 25.7 and 25.9 in *TT* carriers and *AA* carriers, respectively; $P = 0.42$). Among individuals with a low-carbohydrate intake, we observed a mean BMI of 25.4 for *TT* carriers and of 26.8 for *AA* carriers. The increase in BMI across genotypes was mainly restricted to individuals who reported low leisure-time physical activity (P for trend = 0.004, P for interaction = 0.05).

Conclusion: Our results indicate that high-fat diets and low physical activity levels may accentuate the susceptibility to obesity by the *FTO* variant. *Am J Clin Nutr* 2009;90:1418–25.

INTRODUCTION

The increasing prevalence of obesity worldwide is largely influenced by the Western lifestyle, which is characterized by excessive energy intake and low energy expenditure. However, genetic factors may account for different predisposition to obesity between individuals. Genetic variation in the fat mass and obesity–associated gene (*FTO*) locus was recently identified in a genome-wide association study to be associated with obesity (1). The association has been replicated in several populations (2) and is the strongest common genetic predictor of obesity known so far. The *FTO* gene is highly expressed in the hypothalamus, a region involved in appetite regulation, and the *A* allele has been shown to be associated with increased energy intake, especially fat intake (3–5), and impaired satiety responsiveness (6) in children. There is also evidence in adults implicating that the risk-allele carriers consume more energy (7), whereas the genotype does not seem to influence energy expenditure (8, 9). These results indicate that *FTO* is associated with obesity mainly by influencing appetite regulation.

The increased genetic susceptibility of obesity may be modified by environmental factors, particularly physical activity and diet composition. For example, results from several studies suggest that high physical activity may reduce the effect of *FTO* on the risk of obesity (2, 10, 11). In a similar manner, diets with different macronutrient composition (ie, fat, carbohydrate, and protein) and fiber content could influence appetite and satiety (12) and thereby influence the risk.

One major concern when examining the association between diet and obesity in cross-sectional studies is that obesity status may influence the individual's food choice. Studies have indicated that obese individuals generally consume less or the same amount of energy as normal-weight control subjects (13), but studies using the doubly labeled water technique have provided evidence of systematic misreporting of dietary intake among obese individuals (14). Moreover, previous studies have indicated that individuals with reported dietary change in the past generally are more obese and have a lower reported total energy intake than do individuals not reporting food habit changes (15).

The aim of the present study was to examine dietary intake depending on *FTO* genotype and examine whether dietary intakes (macronutrient and fiber intakes) and leisure-time physical activity modify the association between genetic variation in *FTO* and obesity among individuals in the population-based Malmö Diet and Cancer (MDC) cohort. Because the *A* allele has

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been associated with impaired satiety responsiveness and increased fat intake, we hypothesized that fat intake could interact with the *FTO* variant in its effect on body mass index (BMI; in kg/m^2). The availability of detailed data on energy expenditure and dietary data of high validity allowed us to exclude individuals with suspected nonadequate reporting of energy intake (16). We also have the ability to exclude individuals that reported significant dietary change in the past.

SUBJECTS AND METHODS

Study participants and data collection

The MDC study is a population-based prospective cohort (n = 28,449) with baseline examinations conducted from March 1991 to October 1996. All men born between 1923 and 1945 and all women born between 1923 and 1950 and living in Malmö were invited via personal letter or through public advertisements to participate. Limited skills in Swedish and mental incapacity were the only exclusion criteria. All participants visited the study center on 2 occasions. The first visit included detailed instructions about the dietary data collection procedure, distribution of the dietary questionnaire and menu book, and an extensive standardized questionnaire (to collect information on lifestyle, demographic, socioeconomic, and reproductive factors). Nurses conducted anthropometric measurements and collected blood. At the second visit, ≈10 d after the first trained dietary interviewers conducted individual interviews to complete the diet history and to check the correctness of completed questionnaires. In total, 28,098 individuals completed the questionnaire, anthropometric measurements, and dietary assessment.

From November 1991 to February 1994, 6103 subjects were randomly selected from the cohort to participate in a cardiovascular subcohort (MDC-CC). Most of these subjects underwent additional measurements, including the donation of fasting blood. A total of 5135 subjects had both dietary data and had donated fasting blood. After individuals with current use of diabetes mellitus medication or a previous diabetes mellitus diagnosis were excluded, 4999 (2040 men and 2959 women) remained. Of these, 4839 individuals had information on *FTO* genotype and constitute the study population in this article. Ethical approval for the study was obtained from the Ethical Committee at Lund University (LU 51–90).

Dietary data

A modified dietary history method specifically designed for the MDC study was used (17), which combined *1*) a 7-d menu book that collected information on cooked lunches and dinner meals and cold beverages, and *2*) a 168-item dietary questionnaire covering foods regularly consumed during the past year. The participants estimated frequencies of food intake, and usual portion sizes were assessed by using a booklet of photographic aids. Thereafter, during a 1-h interview, the participants were asked questions about food choices, food-preparation practices, and portion sizes of the foods collected in the menu book (using a more extensive book of photos). The interviewer also checked the menu book and dietary questionnaire for overlapping information and for very high reported intakes.

The average daily intake of foods was calculated based on the information available in the menu book (and interview) and the questionnaire. The average daily food intake was converted to nutrient intake data by using the MDC Food and Nutrient Database, which was specifically developed for the MDC study and originated from PC KOST2-93 of the Swedish National Food Administration.

The dietary variables examined in this study were total intake of fat (g/d), carbohydrates (g/d), and protein (g/d); total energy (kcal/d), including energy from fat, carbohydrates, protein, alcohol and fiber; percentage of energy (from nonalcohol and nonfiber energy intake) from fat, carbohydrates, and protein; and fiber density (g fiber/1000 kcal total energy). The relative validity of the dietary method was examined among 105 women and 101 men; 18 d of weighed food records (3 d every second month) collected over 1 y was used as the reference method (18). Energy-adjusted Pearson correlations for fat, carbohydrate, protein, and fiber intakes were in the range of 0.54–0.74.

Misreporting of dietary data

Taking total energy expenditure into account, we can identify individuals that potentially report nonadequate energy intake. We identified such nonadequate reporters of energy by comparing the individually estimated physical activity level (PAL), expressed as energy expenditure divided by basal metabolic rate (BMR), with energy intake divided by BMR. We used equations for predicting BMR from age, sex, weight, and height recommended by the WHO (19), and total energy expenditure for each individual was calculated from self-reported information on physical activity at work, leisure-time physical activity, household work, estimated sleeping hours, self care, and passive time. Hours per day spent on each activity were multiplied by an activity-specific factor to create individual PALs. Nonadequate energy reporters were defined as those with a ratio of reported energy intake to BMR outside the 95% confidence limits of the calculated PAL. The confidence limits for the agreement between energy intake:BMR and the individual PAL were calculated according to recommendations for evaluating "habitual" intake in individuals by Black (20, 21). A 3-category variable was constructed discriminating between underreporters, adequate reporters, and overreporters of energy. Underreporters and overreporters were classified as nonadequate reporters. This procedure is described in detail elsewhere (16).

Individuals with dietary change in the past are suspected to have unstable food habits (15, 22). Dietary change in the past (yes or no) was derived from the questionnaire item, "Have you substantially changed your eating habits because of illness or for some other reason?"

Leisure-time physical activity

Leisure-time physical activity was obtained from a list of different physical activities in the questionnaire (18 items) that were adapted from the Minnesota Leisure Time Physical Activity Instrument (23). Participants were asked to estimate the number of minutes per week, and for each of the 4 seasons, they spent performing 18 different physical activities. The duration of each activity was multiplied by an intensity factor to create a leisure-

time physical activity score. The score was separated into sex-specific tertiles.

The ability of the physical activity questionnaire to rank individuals was examined among 369 subjects against an accelerometer (model 7164; CSA Inc, Shalimar, FL). The accelerometer was monitored for 4 consecutive days, except when sleeping or water-based activities. Spearman's correlation coefficients between the 2 methods were 0.35 in males and 0.24 in females (24).

Anthropometric measurements

Weight (kg) was measured to the nearest 0.1 kg by trained project staff members using a balance-beam scale while the subjects were wearing light clothing and no shoes; height (cm) was measured with a fixed stadiometer calibrated in centimeters. BMI was defined as weight divided by height in square meters (kg/m^2). Obesity was defined as a BMI (in kg/m^2) $\geq$30. Trained project staff members also measured waist and hip circumferences. Bioelectric impedance analysis was used to estimate body composition (single-frequency analyzer, BIA 103; JRL Systems, Detroit, MI). The algorithm used to estimate body fat from impedance was supplied by the manufacturer. Percentage body fat was calculated based on the estimated body fat mass.

Other variables

A variable was created for the seasons of data collection: winter (December–February), spring (March–May), summer (June–August), and fall (September–November). Smoking status was categorized as current smokers (including irregular smoking), ex-smokers, and nonsmokers.

Genotyping

Genotyping of rs9939609 was performed by matrix-assisted laser desorption ionization-time of flight mass spectrometry on the Sequenom MassARRAY platform (San Diego, CA). The rs9939609 was in Hardy-Weinberg equilibrium in the studied population ($P = 0.76$). Genotyping was successful in 4839 (97%) of the subjects.

Statistical methods

SPSS (version 17.0) was used for all statistical analyses. All analyses were performed in *1*) all individuals, *2*) individuals reporting adequate energy intake (ie, nonadequate reporters excluded), and *3*) individuals reporting stable dietary habits (ie, individuals reporting dietary change were excluded). We used chi-square analyses for categorical variables and a general linear model for continuous log-transformed variables to test for trend across *FTO* genotypes, assuming an additive genetic model. Anthropometric factors were adjusted for age and sex. Dietary factors were adjusted for age, sex, and season and for age, sex, season, and BMI.

The subjects were divided into sex-specific tertiles according to the percentage of energy obtained from fat, carbohydrates, and protein and fiber density (g/1000 kcal). In multivariate nutrient-density models, associations of dietary intakes and *FTO* genotype with BMI were evaluated by using general linear models, adjusted for total energy intake, age, sex, and season. We conducted logistic regression to calculate odds ratios (ORs) and 95% CIs of obesity (BMI $\geq$ 30) associated with the *FTO* polymorphism in strata of dietary intake categories (adjusted for energy intake, age, sex, and season) or leisure-time physical activity categories (adjusted for age and sex). For dietary factors, additional adjustments for smoking and tertiles of leisure-time physical activity were performed. For leisure-time physical activity, additional adjustments for smoking and tertiles of carbohydrate intakes were performed. The interaction between dietary factors or leisure-time physical activity and *FTO* genotype was assessed by introducing a multiplicative factor with continuous variables.

RESULTS

Associations between *FTO* and obesity measures

In this population, 12% were obese (BMI $>$ 30). The 17% of the individuals who were homozygous for the risk allele (*A*) had a 1.7-kg higher weight and 0.6-unit higher BMI than did the *TT* carriers. Significant trends for association across *FTO* genotypes for body fat weight ($P = 0.005$), percentage body fat ($P = 0.04$), and waist circumference ($P = 0.01$) were observed (**Table 1**).

Associations between *FTO*, dietary factors, and leisure-time physical activity

We observed a higher frequency of individuals who underreported their dietary energy intake among the *AA* and *AT* genotype carriers than among those with the *TT* genotype (16–17% compared with 14%; $P = 0.02$). Among those with a BMI $>$ 30, 30% of *AA* carriers were categorized as underreporters compared with 20% of *TT* carriers ($P = 0.05$). Moreover, we observed a higher proportion of individuals with a low reported level of leisure-time physical activity among the *AA* carriers than among the *TT* carriers (38% compared with 33%; $P = 0.02$) (Table 1). We observed a lower total energy intake with the *A* allele (2357 kcal for *AA* carriers compared with 2404 kcal for *TT* carriers; $P = 0.05$), and the association was only slightly attenuated after BMI was adjusted for ($P = 0.07$). The difference in energy intake between the genotypes was not significant when nonadequate reporters of energy were excluded (2415 kcal for *AA* carriers compared with 2445 kcal for *TT* carriers; $P = 0.17$). We found a higher percentage of energy from protein for carriers of the *A* allele (15.7 and 16.0 % of energy for *TT* carriers and *AA* carriers, respectively; $P = 0.01$) (Table 1). The significant difference in protein intake remained when the analyses were repeated in adequate energy reporters only ($P = 0.02$), after individuals who reported substantial dietary change in the past were excluded ($P = 0.002$) and after BMI was adjusted for ($P = 0.04$). Among obese adequate reporters, homozygous *A* allele carriers reported a higher amount of energy from fat ($P = 0.03$) and a lower amount from carbohydrates ($P = 0.001$) than did obese subjects not carrying the risk allele.

Interactions between dietary factors, *FTO*, and obesity

The observed increase in BMI across *FTO* genotypes was mainly restricted to those who reported an energy-adjusted high-fat diet, with a mean BMI of 25.3 among *TT* carriers compared with 26.3 among *AA* carriers ($P = 0.0001$) (**Table 2**). We found

TABLE 1
Anthropometric measures, nutrient intakes, and participant characteristics according to *FTO* genotype in the Malmö Diet and Cancer-Cardiovascular Cohort[1]

	FTO genotype			
Variables	*TT* (n = 1673)	*TA* (n = 2336)	*AA* (n = 830)	P for trend[2]
Age (y)	57.7 (57.4, 57.9)[3]	57.3 (57.1, 57.6)	58.0 (57.6, 58.4)	0.16
BMI (kg/m^2)	25.5 (25.3, 25.7)	25.8 (25.6, 25.9)	26.1 (25.8, 26.3)	0.001
Weight (kg)	73.8 (73.3, 74.4)	74.6 (74.1, 75.0)	75.5 (74.7, 76.2)	0.001
Height (cm)	170.1 (169.8, 170.4)	170.2 (169.9, 170.4)	170.2 (169.8, 170.6)	0.87
Waist (cm)	84.4 (83.9, 84.8)	85.0 (84.6, 85.4)	85.5 (84.8, 86.1)	0.01
Fat weight (kg)	19.2 (18.9, 19.5)	19.4 (19.1, 19.7)	20.0 (19.5, 20.4)	0.005
Body fat (%)	25.9 (25.7, 26.2)	26.0 (25.8, 26.2)	26.4 (26.1, 26.7)	0.04
Total energy (kcal/d)	2404 (2375, 2434)	2387 (2362, 2412)	2357 (2317, 2398)	0.05
Carbohydrates (g/d)	258.1 (254.6, 261.6)	255.5 (252.5, 258.6)	252.8 (247.8, 257.7)	0.03
Carbohydrates (% of energy)	45.5 (45.2, 45.8)	45.3 (45.1, 45.6)	45.3 (44.9, 45.7)	0.47
Protein (g/d)	88.0 (87.0, 89.1)	87.3 (86.4, 88.2)	87.5 (86.0, 89.0)	0.64
Protein (% of energy)	15.7 (15.6, 15.8)	15.7 (15.6, 15.8)	16.0 (15.8, 16.1)	0.01
Fat (g/d)	99.9 (98.2, 101.5)	99.5 (98.1, 100.9)	97.4 (95.0, 99.7)	0.07
Fat (% of energy)	38.8 (38.5, 39.1)	39.0 (38.7, 39.2)	38.7 (38.3, 39.2)	0.58
Fiber (g/d)	21.4 (21.0, 21.7)	21.1 (20.8, 21.4)	21.5 (21.0, 22.0)	0.92
Fiber (g/1000 kcal)	9.2 (9.0, 9.3)	9.1 (9.0, 9.2)	9.4 (9.2, 9.6)	0.10
BMI (%)				
<25 kg/m^2	49	48	44	0.02
25–30 kg/m^2	41	40	41	0.91
>30 kg/m^2	10	12	16	0.0002
Leisure-time physical activity (%)				
Low	33	32	38	0.02
Medium	36	33	29	0.001
High	31	35	33	0.23
Reporting dietary change	23	25	23	0.95
Energy reporting (%)				
Under	14	16	17	0.02
Adequate	83	80	80	0.05
Over	3	4	3	0.72

[1] Anthropometric measures were adjusted for age and sex, and nutrient intakes were adjusted for age, sex, and season.
[2] P values for differences in characteristics across *FTO* genotype were based on chi-square tests for categorical variables or on a general linear model for continuous log-transformed variables with the assumption of an additive genetic model.
[3] Adjusted mean; 95% CI in parentheses (all such values).

a significant interaction between fat intake and the genotype on BMI (P = 0.04), which was also observed when the ≈20% of individuals flagged as nonadequate reporters were excluded (P = 0.02) and when individuals reporting a substantial dietary change in the past were excluded (P = 0.005). The *FTO* genotype was associated with a higher BMI among individuals who consumed a diet low in carbohydrates, with mean BMIs of 25.4 and 26.8 for *TT* carriers and *AA* carriers, respectively ($P = 2 \times 10^{-6}$). On the other hand, the *FTO* variant was not associated with a higher BMI among subjects with higher carbohydrate intakes. We observed a significant interaction for carbohydrate intake and genotype for BMI (P = 0.001), which remained after exclusion of nonadequate reporters (P = 0.001) and for individuals who reported dietary changes in the past (P = 0.001). None of the results listed above changed markedly when adjusted for smoking and leisure-time physical activity.

We observed significant interactions between carbohydrate intake and genotype on risk of being obese (BMI > 30; P = 0.0004; **Figure 1**). For example, among individuals with a low carbohydrate intake, *AA* carriers had an OR of 3.11 (95% CI: 2.05, 4.72) for an increased risk of obesity compared with *TT* carriers. This can be compared with an OR of 0.99 (95% CI: 0.62, 1.57) among those who reported a diet high in carbohydrates. We observed a borderline significant interaction between fat intake and genotype on risk of being obese (P = 0.05). Among individuals with a high fat intake, *AA* carriers had an OR of 2.47 (95% CI: 1.59, 3.85) for increased risk of obesity compared with *TT* carriers. This can be compared with an OR of 1.29 (95% CI: 0.85, 1.98) among those who reported a diet low in fat. The test of interaction between fat intake and genotypes was significant when individuals flagged as nonadequate energy reporters were excluded (P = 0.01).

Protein and fiber intakes seemed to modify the association between *FTO* genotype and BMI to a lower degree, and no evidence of an interaction between protein or fiber intake and the *FTO* genotype on BMI was observed (P = 0.39 and P = 0.24, respectively). However, the association between *FTO* genotype and higher BMI was mainly observed among those who consumed a high-protein diet (P = 0.006).

Interaction between leisure-time physical activity, *FTO*, and obesity

The increase in BMI across *FTO* genotypes was mainly restricted to individuals who reported low leisure-time physical activity, and a borderline significant interaction was observed

TABLE 2
Mean BMI by tertile of dietary intake or leisure-time physical activity and *FTO* genotype in the Malmö Diet and Cancer–Cardiovascular cohort[1]

	Mean intakes (range)		No. of subjects by genotype (*TT*/*AT*/*AA*)	Mean (95% CI)			*P* for trend[2]	*P* for interaction[3]	*P* for interaction[3,4]
	Women	Men		*TT*	*AT*	*AA*			
Fat (% of energy)							—	0.04	0.02
Low	31.5 (13.4–35.5)	32.9 (13.9–36.9)	548/762/295	25.7 (25.4, 26.0)	25.8 (25.5, 26.1)	25.9 (25.5, 26.4)	0.42	—	—
Medium	38.0 (35.5–40.6)	39.7 (37.0–42.3)	575/787/255	25.7 (25.4, 26.0)	26.0 (25.7, 26.3)	26.0 (25.5, 26.5)	0.37	—	—
High	44.7 (40.6–58.4)	46.6 (42.3–65.9)	550/787/280	25.3 (24.9, 25.6)	25.6 (25.3, 25.9)	26.3 (25.8, 26.8)	0.0001	—	—
Carbohydrates (% of energy)								0.001	0.001
Low	39.6 (25.2–43.4)	38.1 (22.7–42.2)	557/778/281	25.4 (25.1, 25.7)	25.9 (25.6, 26.1)	26.8 (26.3, 27.2)	2×10^{-6}	—	—
Medium	45.8 (43.5–48.2)	44.8 (42.2–47.4)	556/794/266	25.7 (25.4, 26.0)	26.0 (25.7, 26.3)	25.9 (25.4, 26.4)	0.39	—	—
High	52.5 (48.3–73.2)	51.6 (47.4–69.4)	560/764/283	25.6 (25.3, 25.9)	25.5 (25.3, 25.8)	25.6 (25.1, 26.0)	0.84	—	—
Leisure-time physical activity								0.05	0.10
Low	—	—	542/749/314	25.6 (25.3, 25.9)	26.1 (25.8, 26.4)	26.4 (26.0, 26.9)	0.003	—	—
Medium	—	—	600/756/243	25.4 (25.1, 25.7)	25.5 (25.2, 25.7)	26.1 (25.6–, 26.6)	0.015	—	—
High	—	—	522/814/270	25.5 (25.2, 25.8)	25.7 (25.4, 26.0)	25.6 (25.1, 26.1)	0.97	—	—

[1] Dietary intakes were evaluated by using general linear models, adjusted for total energy intake, age, sex, and season. Physical activity levels were adjusted for age.
[2] *P* values for differences in BMI with the assumption of an additive genetic model.
[3] The interaction was assessed by introducing a multiplicative factor between dietary factors or leisure-time physical activity and *FTO* genotype.
[4] Nonadequate energy reporters were excluded.

($P = 0.05$) between leisure-time physical activity and genotypes. Among individuals with a low level of leisure-time physical activity, we observed a 0.8-unit higher mean BMI for *AA* carriers than for those homozygous for the *T* allele ($P = 0.003$). The *FTO* variant was not associated with a higher BMI among subjects with a high level of leisure-time physical activity ($P = 0.97$). The results did not changed markedly when adjusted for smoking and carbohydrate intake (*P* for interaction = 0.06). No significant sex interactions between diet or leisure-time physical activity and *FTO* on BMI were observed.

Because a high intake of fat was correlated with a low level of leisure-time physical activity in our study, we also examined the BMI differences across *FTO* genotypes with different fat intakes and physical activity levels. Among individuals with low leisure-time physical activity and a high fat intake, we observed a BMI difference between *TT* carriers and *AA* carriers of 1.8 ($P = 0.0003$). However, the difference in mean BMI was only 0.2 between *TT* carriers and *AA* carriers among those with a low level of leisure-time physical activity and a low fat intake ($P = 0.61$) and was 0.7 among those with a high level of leisure-time physical activity and a high fat intake ($P = 0.31$).

DISCUSSION

The present study, conducted among middle-aged individuals in Sweden using dietary data of high validity, indicates that macronutrient composition of the diet may modify the association between the *FTO* variant and obesity, with the effect of the variant mainly restricted to the group of individuals who consumed high-fat and low-carbohydrate diets. We also provide further evidence that low leisure-time physical activity may accentuate the susceptibility for higher BMI by the *FTO* variant.

Unexpectedly, a borderline significantly lower reported energy intake in risk-allele carriers was observed in our study. However, our finding of greater underreporting explains this observation, because no significant difference in energy intake between the different genotype carriers was observed when the nonadequate reporters were excluded from the analysis. In addition, a higher frequency of individuals reporting a low level of leisure-time physical activity was observed among risk-allele carriers, which may contribute to this tendency for lower energy intake among risk-allele carriers. Several earlier studies observed higher energy intakes, especially higher intakes from fat, among *FTO* rs9939609 *AA* genotype carriers (3, 4). However, most of these studies were conducted in children and adolescents. The effect of social desirability (25, 26) and underreporting (27) is probably larger in adults than in children; therefore, the findings in children may be more robust. However, because the difficulties estimating energy intake and energy expenditure with the use of self-reported methods have received much attention (28, 29), and are a major focus of nutrition epidemiology research, the effect of *FTO* variants on energy homeostasis in both children and adults will need to be evaluated by using more precise methods. We focused on relative intakes of macronutrients and observed significant differences in macronutrient intakes between the different genotype carriers, particularly among the obese subjects. In their diet, the obese *AA* carriers reported higher percentages of energy from fat and lower percentages of energy from carbohydrate than did the obese individuals not carrying any *FTO* risk alleles, which supports earlier findings

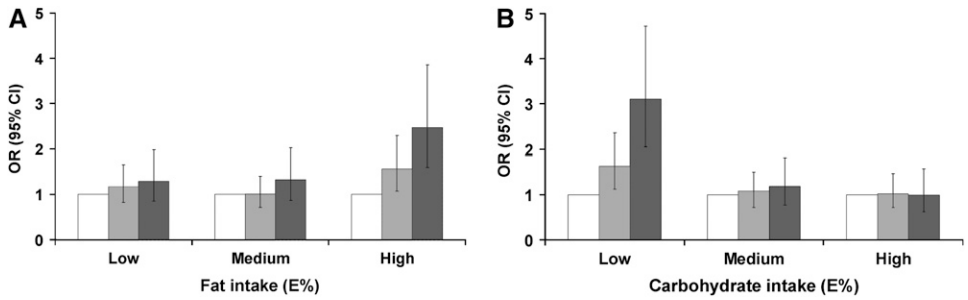

FIGURE 1. Association between *FTO* genotype and obesity in strata of dietary intake categories (fat and carbohydrate intakes as a percentage of energy) in the Malmö Diet and Cancer–Cardiovascular cohort. Logistic regression was used to calculate odds ratios (ORs) and 95% CIs of obesity (BMI $\geq$ 30; in kg/m^2) associated with *FTO* genotypes (*TT*, white bars; *AT*, gray bars; *AA*, black bars) in strata of dietary intake categories adjusted for energy, age, sex, and season. The interaction between dietary factors or leisure-time physical activity and *FTO* genotype was assessed by introducing a multiplicative factor with continuous variables. A: Among individuals with a high fat intake, *AA* carriers had an OR of 2.47 (95% CI: 1.59, 3.85) for increased risk of obesity compared with *TT* carriers (*P* for trend across genotypes = 6×10^{-5}). Among individuals with a low fat intake, *AA* carriers had an OR of 1.29 (95% CI: 0.85, 1.98) for increased risk of obesity compared with *TT* carriers (*P* for trend = 0.21). A borderline significant interaction between fat intake and genotype on risk of being obese was observed (*P* = 0.05). B: Among individuals with a low carbohydrate intake, *AA* carriers had an OR of 3.11 (95% CI: 2.05, 4.72) for increased risk of obesity compared with *TT* carriers (*P* for trend = 1×10^{-7}). This can be compared with an OR of 0.99 (95% CI: 0.62, 1.57) among those reporting a diet high in carbohydrates (*P* for trend = 0.99). We observed significant interactions between carbohydrate intake and genotype on risk of obesity (*P* = 0.0004).

that indicate a preference for fat-rich diets by *FTO* risk-allele carriers (3, 4).

The higher frequency of underreporters among *AA* carriers than among *TT* carriers may represent an important novel observation. Because underreporting of energy intake by individuals with a higher BMI is a common phenomenon, and because the *FTO* risk allele is associated with a higher BMI, the finding that *AA* carriers underreport their energy intake to a higher degree could simply reflect its association with obesity. However, because this issue remained after stratifying for obesity status and because the difference was even more pronounced among those with a BMI $>$ 30, another explanation is warranted. The knowledge concerning systematic underreporting is limited. However, underreporting was previously indicated to be particularly associated with foods high in fat and/or carbohydrates (14) and could be a putative explanation for our findings. Our observation may also be explained if *AA* carriers had a lower than expected estimated energy expenditure because of a metabolic or sympathetic effect of the variant. Interestingly, $FTO^{-/-}$ mice are leaner despite having relative hyperphagia, because they have increased energy expenditure associated with systemic sympathetic activation (30). However, no difference in measured energy expenditure according to *FTO* genotype has been observed in human studies (8, 31). Regarding the exclusion of underreporters, who constituted $\approx$20% of all individuals and 80% of all nonadequate reporters, generally stronger effects were observed.

The *FTO* polymorphism has been associated with obesity in most of the examined populations, despite differences in allele frequency of the high-risk variants and the linkage disequilibrium structure of the region between populations. Our results support the hypothesis that the *FTO* variant would likely be higher in a population with a Western lifestyle characterized by an energy-dense diet and a sedentary lifestyle than in a population with a diet lower in fat content and with a higher degree of physical activity (32). Whether the lack of such an obesogenic environment explains the lack of association between the *FTO* variant and obesity in some of the studies in Asian and African populations remains to be shown (33–35).

Most studies that investigated the association between *FTO* genotype and physical activity have observed no or weak associations (5, 8, 9, 36). More importantly, several studies have observed an interaction between physical activity and *FTO* genotype on the association with BMI. For example, among physically passive individuals, Andreasen et al (2) observed a 1.95-unit higher mean BMI for individuals homozygous for the *A* allele than for those homozygous for the *T* allele. The mean difference in BMI among individuals with a high or very high physical activity was only 0.47. Although the validity of the physical activity variable may be uncertain because it is self-reported, our study successfully repeated these earlier results that the association between *FTO* genotype and increased BMI was mainly restricted to individuals with a low physical activity.

Our study had some limitations that need to be discussed. Our study was based on an analysis of cross-sectional data, which limits the ability to investigate causality. In addition, some of the associations may have been attenuated by imprecision of dietary intake and physical activity measurements, including the limited extent to which short-term measures reflect long-term dietary and lifestyle patterns. Because diet choices may be the result of both genetic factors and obesity status, and because certain lifestyle factors may be associated with diet, spurious associations may emerge. Thus, the results of analyses with adjustments for multiple factors should be interpreted with caution. In addition, when associations between any factor and different macronutrient intakes are compared, it needs to be kept in mind that a stronger effect of fat and carbohydrate intakes than of protein intake may be observed because of the relatively larger intake range of fat and carbohydrates compared with the homogenous protein intakes. Moreover, we were unable to examine the effect of genotype among individuals with extreme diets, such as diets very low in carbohydrates, because the lowest reported carbohydrate content of an individual in this population was as high as 23% of energy. Finally, multiple tests were performed, and some of the observed significant associations and interactions could have been due to chance and need to be replicated. However, the findings agree with our hypothesis that an obesogenic environment (ie, a high fat intake and a low physical activity) may accentuate the association between *FTO* genotype and obesity.

Our study highlights the possibility that genetic susceptibility to obesity may be modified by environmental factors including

diet and could in the future contribute to personalized dietary advice. From a public health perspective, it can be speculated that a reduction in overall fat consumption in the population and an increase in the level of physical activity could minimize the effect of this genetic susceptibility factor on obesity status. For example, no increased risk of obesity was observed among individuals who consumed <41% of energy from fat in our study. Moreover, the *FTO A* allele had a minimal effect on BMI among individuals who reported a high leisure-time physical activity.

FTO explained only a small part of the genetic susceptibility to obesity in the population, and several other obesity genes have recently been identified (37–39). As for *FTO*, many of the novel genes are highly expressed in the hypothalamus and few (eg, *SH2B1* and *BDNF*) have a clear role in appetite control, as shown in knockout models that develop hyperphagia and obesity (40, 41). However, the mechanisms by which most of these genes, particularly common variations in noncoding regions, can affect appetite control or in other means contribute to obesity in humans still remain to be explained.

Herein we propose an important role for both diet composition and physical activity in modifying the susceptibility of developing obesity by the common variant in *FTO*. Future studies using dietary data of high quality are warranted to further define whether, how, and to what degree the genetic risk by *FTO*—or other obesity-susceptibility genes—can be modified by lifestyle factors aiming for individualized lifestyle advice to prevent obesity in genetically predisposed individuals.

The authors' responsibilities were as follows—ES: conducted the statistical analysis and wrote the manuscript; and BG: assisted with the statistical analyses. All authors contributed to the analytic design, data interpretation, revision of the manuscript, and final approval of the manuscript. None of the authors had any conflicts of interest.

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