Sport Sciences for Health (2019) 15:689–697
https://doi.org/10.1007/s11332-019-00587-5

ORIGINAL ARTICLE

Very light physical activity amount in *FTO* genetically predisposed obese individuals

Giuseppe Labruna[1] · Maurizio Marra[2] · Carmela Nardelli[3,4] · Annamaria Mancini[1,4,5] · Pasqualina Buono[1,4,5] · Lucia Sacchetti[4] · Fabrizio Pasanisi[2]

Received: 30 May 2019 / Accepted: 27 August 2019 / Published online: 9 September 2019
© Springer-Verlag Italia S.r.l., part of Springer Nature 2019

Abstract

Purpose Fat mass and obesity-related (*FTO*) rs9939609 polymorphism has a role in body mass index (BMI) increase and in predisposing to metabolic syndrome (MetS). Our aim was to investigate if a very light physical activity could counteract weight gain and MetS in obese subjects bearing the rs9939609 *FTO* polymorphism from Southern Italy.

Methods Data of fitness components, anthropometry, clinical-biochemical parameters and *FTO* polymorphism in 78 unrelated morbid obese subjects from Southern Italy (15–30 years) were examined. Physical activity energy expenditure was monitored by a SenseWear Pro 3 Armband for 24 h/day for 2 consecutive weekdays in all enrolled individuals.

Results Sedentary obese subjects had higher waist circumference (124.8 vs 117.9 cm, $P < 0.05$), BMI (43.4 vs 37.7 kg/m^2, $P < 0.0001$) and fat mass (49.2 vs 44.5%, $P < 0.0001$) compared to lightly active ones. Further, lightly active obese subjects bearing the rs9939609 *FTO* minor allele had a lower BMI than polymorphic sedentary ones (37.1 vs 45.3 kg/m^2, respectively, $P < 0.01$), and did not differ in metabolic syndrome presence.

Conclusion Our results suggest that a very light amount of physical exercise is associated with a lower BMI in obese subjects bearing the minor allele of the rs9939609 *FTO* polymorphism.

Keywords Very light intensity exercise · Obesity · BMI · *FTO* polymorphism · Metabolic syndrome

Introduction

According to the last reports, worldwide obesity has nearly tripled since 1975 being overweight 39% and obese 13% of adults aged 18 years and over in 2016 [1]. A similar obesity incidence was observed in Southern Italy where more than 10% of adult population is affected by obesity, with an increment in the prevalence of the disease among children especially in Campania region [2, 3]. Beside the genetic background that exerts a role in the regulation of body weight, in obesity itself and/or in the development of obesity-related diseases [4–9], a clear influence of environmental and behavioral changes on obesity epidemic has also been described [9, 10].

According to the World Health Organization's (WHO) guidelines concerning physical activity, adults aged 18–64 years should perform at least 150 min of moderate-intensity aerobic physical activity throughout the week, or do at least 75 min of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity [11]. Sedentary behavior has become a leading risk factor for ill health: 1 million deaths (about 10% of the total) and 8.3 million disability-adjusted life years lost per year in the WHO European Region are attributable to inactivity [11]. Based on the study by Gerovasili et al., only 52.6% of the Italian population could be classified as adequately to highly active, meeting

✉ Lucia Sacchetti
sacchett@unina.it

✉ Fabrizio Pasanisi
pasanisi@unina.it

[1] IRCCS SDN, Naples, Italy

[2] Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II, Naples, Italy

[3] Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II, Naples, Italy

[4] CEINGE-Biotecnologie Avanzate, Naples, Italy

[5] Dipartimento di Scienze Motorie e del Benessere, Università degli Studi di Napoli Parthenope, Naples, Italy

the WHO's criteria [12]. Walking represents an easy way to engage moderate physical activity, and a minimum of 7000 steps/day has been suggested for healthy young adults to improve health by modifying body composition [13]. It has been shown that moderate physical activity reduced the presence of MetS or single MetS risk factors independent of potential confounders [14–17]. In contrast, the total sedentary time has been associated with clustered metabolic risk factors and/or single components of the MetS [16].

Concerning the genetic aspects, among the hundreds of gene variations so far identified having a role in body mass index (BMI) regulation [18, 19], the rs9939609 T > A *FTO* polymorphism was extensively studied and clearly correlated with body fat accumulation [20]. Moreover, our group previously described a role for this variation in predisposing obese patients toward the metabolic syndrome (MetS), a cluster of factors that increase the risk of obese patients for diabetes and cardiovascular diseases [21]. Further, the reduction observed in the last decades in energy expenditure, mainly related to a more sedentary lifestyle, and to the change in the alimentary behavior could have profound long-term effects on body weight regulation [22]. Globally, physical activity, together with dietary intervention, represent the most important strategies in primary health care aimed to counteract weight gain [9].

Based on literature data suggesting low physical activity accelerates the effect of *FTO* polymorphism on fat accumulation in the human healthy subjects [23], we hypothesized that a very light physical activity could impact weight gain and MetS presence in our obese subjects.

In this study we aimed to investigate if a very light physical activity was associated with less BMI and MetS presence in obese subjects bearing the rs9939609 *FTO* polymorphism.

Materials and methods

Subjects

One thousand morbidly obese subjects, recruited at the Obesity Outpatient Clinic of the Department of Clinical and Experimental Medicine, University of Naples Federico II (Italy), were previously investigated for obesity-associated genetic polymorphisms, including rs9939609 *FTO* polymorphism [21]. From this population, we selected the first one hundred unrelated obese individuals in the age range from 15 to 30 years available to undergo the physical activity monitoring by the SenseWear Pro 3 Armband (BodyMedia Inc., Pittsburgh, PA, USA). Obese subjects aged < 21–22 years were considered post-pubertal according to the Tanner scale (V). The physical activity amount was evaluated within a week from the enrollment.

Twenty-two subjects did not comply in wearing the armband and were not considered for the study and their data excluded from the analysis. A total of 78 patients were included in the present study. All patients or their parents gave the written informed consent to the study that was conducted according to the Helsinki II Declaration and was approved by the Ethics Committee of the Federico II University (authorization no. 193/06, October 25, 2006; amendment no. 193/06/ESES1, October 1, 2014). Inclusion criteria were: BMI > 35 kg/m^2, absence of: thyroid disease, viral infections, diabetes, cancer and drug therapies for hypertension and/or hyperlipidemia.

Anthropometric, metabolic, and biochemical measures

For all the enrolled subjects, the following parameters were measured: body weight (kg), height (m) and waist circumference (cm); fat mass (FM) and fat free mass (FFM) % (by Bioimpedence Analysis, Sta/BIA Akern, Florence, Italy); respiratory quotients (RQ) and resting metabolic rate (RMR) (by indirect calorimetry, Sensor Medics Vmax29, Anaheim, CA, USA). Hydration status in each enrolled subject was verified, in fact no significant change (< 2%) in body weight was observed in the morning in the 48 h monitoring time [24].

Clinical–biochemical parameters were evaluated by routine laboratory methods (reagents and equipments from Roche, Cobas 6000; Roche Diagnostics S.p.A., Monza, Italy).

Genetic analysis

Genomic DNA was extracted from peripheral blood samples with the Nucleon BACC2 kit (Amersham Life Science, Little Chalfont, Bucks, UK) and the *FTO* rs9939609 T > A polymorphism was investigated by TaqMan analysis (Applied Biosystems, Foster City, CA, USA) as previously described [21]. Briefly, two probes were used in a biallelic system; one probe is specific for the wild-type allele and the other is complementary to the mutant allele. The alleles were discriminated with fluorogenic probes, which consist of an oligonucleotide with a fluorescent reporter dye (VIC or FAM), a non-fluorescent quencher and a minor groove binder (MGB). The latter molecule forms a hyperstabilized duplex with complementary DNA thereby increasing the capacity of the hybridization probe to discriminate the SNP.

In a sub-group (27/78 subjects) of the study population we also collected data on alimentary habit by a weekly food diary filled in by individuals under the supervision of an experienced dietitian.

MetS assessment

MetS was diagnosed measuring the presence of three out of five risk factors, namely high waist circumference, hyperglycemia, hypertriglyceridemia, hypertension and hypo-HDL-cholesterolemia, according to the AHA criteria (i.e.: waist circumference ≥ 102 cm in men and ≥ 88 cm in women, glycemia ≥ 5.5 mmol/L, triglyceridemia ≥ 1.7 mmol/L, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mm Hg, and HDL-cholesterolemia < 1.03 mmol/L in men and < 1.29 mmol/L in women) [25]. Homeostasis model assessment (HOMA) index was calculated by the formula: fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5. We also calculated the fatty liver index (FLI), as a surrogate measure of hepatic functions impairment, according to the formula: $FLI = (e^{0.953\times\ln(\text{triglycerides})+0.139\times BMI+0.718\times\ln(GGT)})/(1+e^{0.953\times\ln(\text{triglycerides})+0.139\times BMI+0.718\times\ln(GGT)})\times 100$ [26].

Physical activity monitoring

All the enrolled patients were asked to wear a SenseWear Pro 3 Armband (BodyMedia Inc., Pittsburgh, PA, USA) for 24 h/day for 2 consecutive weekdays, during which they did not change their usual daily life activities. The wearable instrument is a reliable tool for the assessment of energy expenditure in normal daily life in absence of high-intensity physical activity [27].

A 48 h monitoring time was chosen because a longer time was not well accepted by all patients, especially by the younger ones. None of the young patients engaged in non-endurance activity (resistance training/anaerobic sports) during the observation.

The SenseWear Armband is a body monitor, worn over the triceps muscle of the not-dominant arm, that measure heat flux, galvanic skin response and skin temperature. Moreover, by a two-axis accelerometer, also the daily steps number is recorded. By combining data from all these sensors and age, sex, body weight and height of the examined subject, using an algorithm developed by the manufacturer (SenseWear Professional software, v 6.1, BodyMedia Inc.) it is possible to estimate the mean total daily energy expenditure (TDEE), the active daily energy expenditure (ADEE), physical activity duration (PAD), sedentary behavior and sleep duration. The instrument also calculates the median daily metabolic equivalent of the task (MET), corresponding to body oxygen consumption in 1 minute during rest, with one MET equals ~ 3.5 mL O_2/kg/min in adults weighing 70 kg [28].

In our population the MET ranged from 0.7 to 2.2 and the median value was 1.2, the latter corresponding to ~ 7600 steps. Considering that this value is near the lower end of 7000–13,000 steps/day proposed for a healthy lifestyle in young adults, we arbitrary chose this cutoff for indicating as sedentary those subjects with MET < 1.2 and lightly active those with MET > 1.2 [13]. Our choice was also in agreement to that previously reported in another cohort performing light physical activity [29].

Statistics

Kolmogorov–Smirnov test was used to verify the normal shape distribution of the tested variables, and the Student's *t* test was used for inter-groups comparison. χ^2 test was used for dichotomic variables comparison and to verify the Hardy–Weinberg equilibrium of the genotype frequencies. Pearson partial correlation test and linear regression analyses were used to explore inter-variables associations. ANCOVA was used to explore any difference in BMI levels between wild type and polymorphic *FTO* subjects and between sedentary and lightly active individuals controlling for age and sex effects on the dependent variable (BMI). Linear multivariate regression analysis was used to investigate the association between the *FTO* genetic background, physical activity, anthropometric characteristics and the BMI (dependent variable), after correction for age and sex in the tested subjects. A pre-hoc power calculation analysis to explore if the number of the studied obese individuals was sufficient for testing our hypothesis was performed using G*Power calculator (version 3.1.9.2, Franz Faul, Universitat Kiel, Germany). After imputing the following parameters: effect size = 0.05; α error = 0.05 (two variables); number of groups = 2; power = 0.87, we obtained the total sample size = 77.

Results were considered statistically significant at a *P* value lower than 0.05 after Bonferroni correction. Statistical analysis was performed using SPSS 18.0 (SPSS Inc. Headquarters, Chicago, Ill, USA).

Results

Clinical, anthropometric characteristics and biochemical profiles of obese subjects

Mean age and BMI ± SEM of the studied population (39.7% males) were: 18.5 ± 0.3 years (males: 17.9 ± 0.5 years; females: 19.5 ± 0.7 years); 40.6 ± 0.8 kg/m^2 (males: 40.8 ± 1.2 kg/m^2; females: 39.3 ± 1.1 kg/m^2). Clinical and anthropometric characteristics and biochemical profiles of obese patients are reported in Table 1a/b.

Table 1 a. Clinical, anthropometric, and biochemical characteristics of the studied subjects. b. Energy expenditure and physical activity as measured by SenseWear Armband

	M ($n=31$)		F ($n=47$)		P
	Mean	SEM	Mean	SEM	
a					
Age (years)	17.9	0.5	19.5	0.7	
Weight at the birth (kg)	3.6	0.2	3.5	0.1	
BMI (kg/m^2)	40.8	1.2	39.3	1.1	
WC (cm)	127.7	2.4	117.0	1.9	0.001
RQ	0.894	0.014	0.866	0.028	
RMR (kcal/day)	2642.6	63.0	2015.8	42.0	0.0001
FFM (%)	54.9	1.3	51.7	0.8	0.006
FM (%)	45.1	1.3	48.3	0.8	0.006
SBP (mm/Hg)	121.0	1.6	117.3	1.1	
DBP (mm/Hg)	78.1	1.2	75.3	0.9	
MetS (%)	54.5		45.5		
Hearth rate (bpm)	75.5	1.4	76.8	1.4	
Glucose (mmol/L)	4.3	0.1	4.2	0.1	
Total cholesterol (mmol/L)	4.2	0.1	4.2	0.1	
HDL cholesterol (mmol/L)	1.1	0.01	1.3	0.01	0.01
Triglycerides (mmol/L)	1.4	0.1	1.2	0.1	
AST (U/L)	28.9	2.4	20.4	0.9	0.002
ALT (U/L)	44.2	5.5	26.6	2.3	0.005
ALP (U/L)	105.8	8.9	80.3	3.2	0.010
GGT (U/L)	26.6	2.0	25.5	6.0	
CHE (U/L)	1,0015.5	269.5	8861.8	213.7	0.001
Total bilirubin (umol/L)	11.5	1.2	9.1	0.6	
Uric acid (mmol/L)	0.4	0.001	0.3	0.001	
ALB (g/dL)	4.7	0.01	4.5	0.01	0.01
TP (g/dL)	7.7	0.1	7.6	0.1	
Creatinine (umol/L)	75.85	2.49	62.63	1.28	0.0001
Urea (mmol/L)	5.0	0.1	4.5	0.1	
Insulin	21.7	2.3	16.4	1.8	0.03
HOMA	4.25	0.43	3.07	0.32	0.03
FLI	93.2	1.9	84.9	2.5	0.01
b.					
TDEE (kcal/day)	3748.8	106.5	2784.7	83.7	0.0001
ADEE (kcal/day)	704.5	77.6	435.7	53.6	0.004
TDEE–ADEE (kcal/day)	3044.3	103.9	2349.0	64.8	0.0001
PAD (h/day)	1.3	0.2	1.0	0.1	
Steps (n)	8729.5	830.7	7875.4	491.0	
METs	1.3	0.04	1.2	0.05	
Sedentary behavior (h/day)	7.8	0.5	7.2	0.4	
Sleep duration (h/day)	5.7	0.4	5.9	0.3	

BMI body mass index, *WC* waist circumference, *RQ* respiratory quotient, *RMR* resting metabolic rate, *FFM* fat free mass, *FM* fat mass, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MetS* metabolic syndrome, *ALB* albumin, *TP* total proteins, *HOMA* homeostasis model assessment, *FLI* fatty liver index, *TDEE* total daily energy expenditure, *ADEE* active daily energy expenditure, *PAD* physical activity duration, *METs* metabolic equivalents

MetS assessment

MetS was observed in 19.3% male and 10.6% female obese patients. In addition to abdominal obesity, low HDL-Cholesterolemia was the most prevalent component of MetS both in males and in females (100% of males and females), followed by hypertriglyceridemia (90% of males and 80% of females) and hypertension (50% of males and 60% of females), whereas hyperglycemia was found in 20% of females.

Energy expenditure and physical activity monitoring

Energy expenditure and physical activity as measured by SenseWear Pro 3 Armband are reported in Tables 1b and 2b. Gender-related differences were observed for TDEE, ADEE, and TDEE-ADEE, $P<0.004$ (Table 1b).

Pearson partial correlation analysis, after correction for sex, age and *FTO* polymorphism presence, showed a positive correlation between METs and: FFM% ($r=0.4$, $P=0.001$), ADEE ($r=0.7$, $P<0.0001$), PAD ($r=0.7$, $P<0.0001$), and daily steps number ($r=0.6$, $P<0.0001$) (Table 3). METs was also negatively correlated to BMI ($r=-0.5$, $P<0.0001$), waist circumference ($r=-0.4$, $P=0.001$), FM% ($r=-0.4$, $P=0.001$) and to FLI ($r=-0.3$, $P=0.008$) (Table 3).

The number of patients positive for MetS was equally distributed between METs ≤ 1.2 and METs >1.2 groups (14% vs 13%, $P=$ ns at χ^2 test), but sedentary obese subjects compared to very lightly active obese subjects had a higher waist circumference (124.8 vs 117.9 cm, $P<0.05$), a higher BMI (43.4 vs 37.7 kg/m^2, $P<0.0001$), higher FM % (49.2 vs 44.5%, $P<0.0001$) and FLI (91.7 vs 83.2, $P=0.02$) and lower FFM % (50.8 vs 55.5%, $P<0.0001$) (Table 2a). Similar significant results were obtained when dividing the population based on gender (data not shown). However, no significant difference was observed between the two groups of patients at χ^2 test in gender distribution and in the presence of the different features of MetS (Table 2a).

Dietary habit was available in 27 out 78 obese patients, equally distributed in the two sedentary and lightly active obese groups. 89% of individuals who filled in the diary were polymorphic for the *FTO* SNP, a percentage slightly higher than that of polymorphic subjects (73%) lacking the dietary habit information ($P=$ ns at χ^2 test). Self-reported calorie intake and meal composition did not differ between the two groups (data not shown).

Table 2 a. Clinical, anthropometric, and biochemical characteristics of the studied subjects. b. Energy expenditure and physical activity as measured by SenseWear Armband

	METs ≤ 1.2 ($n=44$)		METs > 1.2 ($n=34$)		*P*
	Mean	SEM	Mean	SEM	
a.					
Female (%)	46.0		54.0		
Age (years)	19.2	0.5	17.7	0.7	
Weight at the birth (kg)	3.5	0.1	3.5	0.1	
BMI (kg/m^2)	43.4	1.1	37.7	0.9	0.0001
WC (cm)	124.8	2.2	117.9	2.1	0.03
RQ	0.9	0.0	0.8	0.0	
RMR (kcal/day)	2302.8	68.5	2335.0	86.0	
FFM (%)	50.8	0.8	55.5	0.9	0.0001
FM (%)	49.2	0.8	44.5	0.9	0.0001
SBP (mm/Hg)	119.2	1.2	118.8	1.6	
DBP (mm/Hg)	77.1	1.0	75.9	1.2	
MetS (%)	60.0		40.0		
Hearth rate (bpm)	77.1	1.5	75.3	1.6	
Glucose (mmol/L)	4.3	0.1	4.2	0.1	
Total cholesterol (mmol/L)	4.4	0.1	4.1	0.1	
HDL cholesterol (mmo/L)	1.2	0.0	1.2	0.1	
Triglycerides (mmol/L)	1.4	0.1	1.3	0.1	
AST (U/L)	24.6	1.9	23.6	1.7	
ALT (U/L)	35.4	3.9	32.3	4.5	
ALP (U/L)	84.8	3.5	92.1	8.0	
GGT (U/L)	30.1	6.7	22.6	2.2	
CHE (U/L)	9438.9	250.4	9239.2	262.2	
Total bilirubin (umol/L)	10.4	1.0	9.7	0.8	
Uric acid (mmol/L)	0.3	0.001	0.4	0.001	
ALB (g/dL)	4.6	0. 01	4.7	0. 01	0.02
TP (g/dL)	7.7	0.1	7.7	0.1	
Creatinine (umol/L)	69.0	1.9	68.0	2.7	
Urea (mmol/L)	4.6	0.2	4.7	0.2	
Insulin	20.1	2.2	16.9	1.9	
HOMA	3.9	0.4	3.2	0.4	
FLI	91.7	1.7	83.2	3.3	0.02
b.					
TDEE (kcal/day)	3013.9	93.3	3391.5	155.2	0.03
ADEE (kcal/day)	348.8	37.5	818.1	75.7	< 0.0001
TDEE–ADEE (kcal/day)	2665.1	78.3	2573.4	128.1	
PAD (h/day)	0.7	0.1	1.7	0.2	< 0.0001
Steps (*n*)	6536.4	457.2	10,593.0	634.3	< 0.0001
METs	1.0	0.02	1.5	0.04	< 0.0001
Sedentary behavior (h/day)	7.8	0.4	7.0	0.4	
Sleep duration (h/day)	6.0	0.4	5.5	0.3	

BMI body mass index, *WC* waist circumference, *RQ* respiratory quotient, *RMR* resting metabolic rate, *FFM* fat free mass, *FM* fat mass, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MetS* metabolic syndrome, *ALB* albumin, *TP* total proteins, *HOMA* homeostasis model assessment, *FLI* fatty liver index, *TDEE* total daily energy expenditure, *ADEE* active daily energy expenditure, *PAD* physical activity duration, *METs* metabolic equivalents

Table 3 Pearson partial correlation analysis, after correction for sex, age and *FTO* polymorphism presence, between energy expenditure, physical activity and anthropometric characteristics of the study group ($n=78$)

	TDEE	ADEE	PAD	Steps	METs
BMI					
r	0.3	–	–	−0.3	−0.5
P	0.01	–	–	0.011	<0.0001
WC					
r	0.3	–	−0.3	−0.3	−0.4
P	0.016	–	0.050	0.035	0.001
FFM					
r	–	–	–	0.3	0.4
P	–	–	–	0.031	0.001
FM					
r	–	–	–	−0.3	−0.4
P	–	–	–	0.031	0.001
TDEE					
r	–	0.5	0.3	0.4	–
P	–	<0.0001	0.023	0.003	–
ADEE					
r	0.5	–	0.9	0.8	0.7
P	< 0.0001	–	<0.0001	<0.0001	<0.0001
TDEE–ADEE					
r	0.8	–	−0.3	–	−0.3
P	< 0.0001	–	0.032	–	0.005
PAD					
r	0.3	0.9	–	0.7	0.7
P	0.023	<0.0001	–	<0.0001	<0.0001
Daily steps number					
r	0.4	0.8	0.7	–	0.6
P	0.003	<0.0001	<0.0001	–	<0.0001
METs					
r	–	0.7	0.7	0.7	–
P	–	<0.0001	<0.0001	<0.0001	–
FLI					
r	–	–	–	−0.3	−0.3
P	–	–	–	0.050	0.008

Only statistically significant correlations are reported

BMI body mass index, *WC* waist circumference, *FFM* fat free mass, *FM* fat mass, *TDEE* total daily energy expenditure, *ADEE* active daily energy expenditure, *PAD* physical activity duration, *METs* metabolic equivalents, *FLI* fatty liver index

Association between rs9939609 T > A FTO polymorphism, physical activity and BMI

The frequencies of the rs9939609 T > A *FTO* polymorphism were: 22.6% wild-type homozygous; 53.2% heterozygous; 24.2% polymorphic homozygous. Genotype frequencies met the Hardy–Weinberg equilibrium. The distribution of polymorphic subjects did not differ between

sedentary and very light active subjects (74% vs 79%, respectively; P = ns at χ^2 test). A slightly higher prevalence of polymorphic subjects was observed among patients with MetS compared to MetS-negative patients (90% vs 75%, P = ns at χ^2 test). Sedentary obese subjects bearing the *FTO* polymorphic allele (heterozygous + homozygous individuals) had a higher BMI than wild-type ones (45.3 vs 39.8 kg/m^2, $P = 0.01$), with a mean increment of about 3 kg/m^2 per polymorphic allele. This difference was not observed between wild type and polymorphic very light active subjects (Fig. 1).

Polymorphic lightly active obese individuals showed a lower BMI (mean reduction ~ 18%) than polymorphic sedentary ones (37.1 vs 45.3 kg/m^2, $P < 0.0001$) (Fig. 1). The BMI reduction remained significant after correction for age and sex by ANCOVA test ($F = 5.38$, corrected $R^2 = 0.203$, $P = 0.034$). The linear multivariate regression analysis confirmed that, after correction for gender and age, METs values were strongly negatively associated with BMI ($\beta = -0.48$, $P = 0.001$), independently from the *FTO* polymorphism (Pearson correlation coefficient, $r = -0.064$, P = ns).

Discussion

Despite a similar frequency of the *FTO* polymorphism was observed in the two METs groups (74% and 79% in sedentary and lightly active individuals, respectively), the lightly active individuals had a lower BMI than the sedentary ones of about 18%. Our data are in agreement to those reported in three independent meta-analysis conducted on more than 218,000 subjects of different age ranges and from different geographical area [30–32] demonstrating that an active lifestyle is associated to a reduction of BMI in *FTO* genetically predisposed subjects. In addition, reduction by 30–70% of obesity-related traits was previously reported in polymorphic *FTO* physically active compared to sedentary adult obese subjects [30, 32–35].

Accordingly, we found a strong inverse correlation between very light physical activity and markers of adiposity after controlling for sex and age in our study cohort. In fact, lightly active subjects had reduced waist circumference, BMI and FM%. Our data are in accordance to those of Myers et al. that reported a negative correlation between very light physical activity and markers of adiposity [36]. Moreover, lightly physical active group had a lower FLI than the sedentary group, suggesting a low hepatic impairment in obese patients engaged in very light physical activity. Our finding agrees with recently reviewed data in an age-matched population [37] demonstrating that physical activity has a positive impact on hepatic markers improvement. Interestingly, we previously described a more favorable metabolic status associated to an enhanced insulin response in obese patients with low FLI [7, 38].

In our obese patients, the MetS prevalence was 19.3% and 10.6% in male and female patients, respectively. These data were quite similar to those reported in patients with the same age range than ours (14–15%) [39–41], but lower than those reported for other older investigated groups both by us and by other researchers, ranging from 34 to 53% [7, 39, 42, 43]. Likely, the youth of our cohort (mean age lower than 18 and 19 years, in males and females, respectively) explained the low

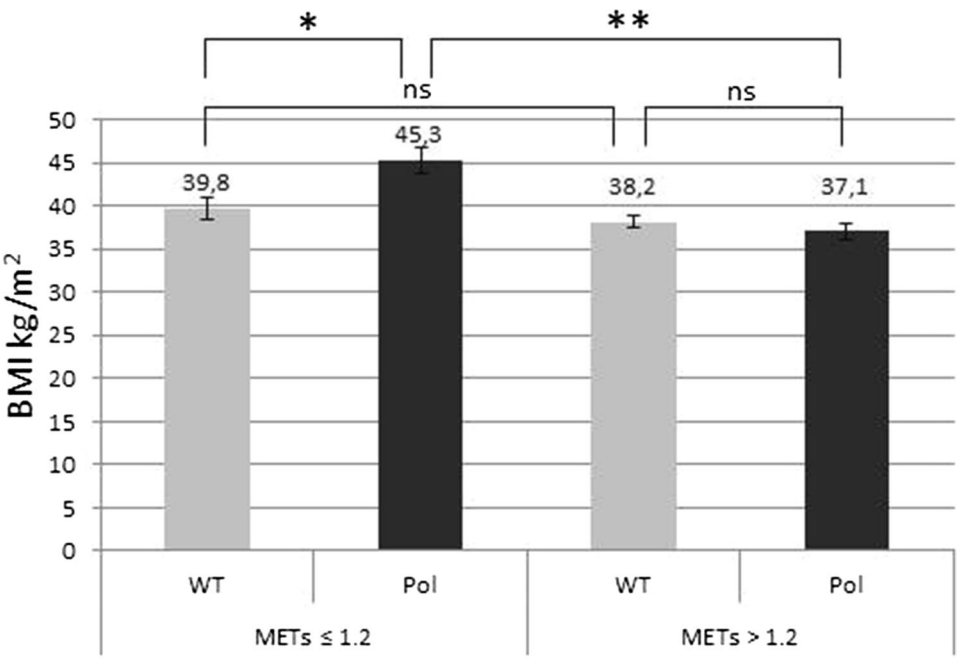

Fig. 1 Relationship between physical activity and BMI in obese patients according to the presence/absence of rs9939609 *FTO* polymorphism. Physical activity significantly reduced the BMI (18%) in polymorphic obese patients. Bars represent SEM. *WT* wild-type patients, *Pol* polymorphic patients (heterozygous + homozygous), *METs ≤ 1.2* sedentary patients, *METs > 1.2* lightly active patients, *ns* not statistically significant; *$P < 0.05$; **$P < 0.0001$

MetS presence. Accordingly, an age effect on the prevalence of MetS independently from obesity presence was recently described [40, 43].

In a larger and older than the present obese population ($n = 1000$, mean age = 32.6 years) we previously demonstrated that the rs9939609 *FTO* minor allele was a strong risk factor for MetS, accounting for about 21% of the syndrome [21]. The low prevalence of MetS in our young obese population could explain the lack of association between the rs9939609 *FTO* polymorphism and MetS, even if a slightly higher prevalence of the rs9939609 *FTO* minor allele was observed among MetS-positive than in MetS-negative patients (90% vs 75%).

Concerning the interaction of physical activity and *FTO* genotype, our data agree with some studies reporting that this lifestyle factor might reduce the effect of *FTO* polymorphism on body weight and body composition [32, 44, 45]. Globally, there is not yet agreement on the mechanism of *FTO* impact on obesity, several experimental evidences observed a positive relationship between *FTO* gene mRNA levels in subcutaneous fat tissue and BMI [23]. Furthermore, a possible role for the *FTO* gene in metabolism of adipose tissue has also been described, suggesting that individuals carrying the *FTO* obesity-associated risk allele have less lipolysis in adipocytes [46].

Some limitations exist concerning our study. First of all, we studied adolescent (Tanner scale V) and adult obese individuals all together, but we verified post-pubertal state by Tanner scale and observed no difference between adolescent and adult obese subjects in anthropometric measurements, nor in markers of liver functionality, in glucose and lipid metabolism (data not shown). Our decision was also supported by literature data [47]. In fact, an early growth acceleration was observed in young obese subjects, representing itself in children a predictor of childhood obesity [47].

Second, we recorded the physical activity in only 2 consecutive weekdays. The 48 h-window-monitoring time was chosen because a longer time was not well accepted by all patients, especially by the younger ones. So we preferred this limited observation time to the less accurate self-reported data as previously highlighted [48, 49].

Considering the influence of ethnic background in the association between gene polymorphisms and diseases, a strength of our study is the great homogeneity of the investigated population, in terms of the geographic area of origin, Southern Italy, the high degree of obesity considered and the young age of the studied subjects.

Conclusions

Our findings support our hypothesis that lightly active individuals bearing the rs9939609 *FTO* minor allele had a lower BMI than polymorphic sedentary ones. Further longitudinal studies are required to assess the causality link between very light physical activity and less weight gain in young genetically predisposed obese subjects.

Funding Pasqualina Buono was supported by the University of Naples "Parthenope" under grants "Bando per la Ricerca competitiva, triennio 2016-18 quota C" and "Fondo per la ricerca individuale di Ateneo, Annualità 2016". Grants: Progetto Regione Campania SATIN to Lucia Sacchetti.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical approval All procedures were in accord with current national and international laws and regulations governing in line with the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. WHO (2018) https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
2. ISS (2016) http://www.epicentro.iss.it/okkioallasalute/dati2016.asp
3. Saba A, Cupellaro E, Vassallo M (2014) Which dimensions of food-related lifestyle are likely to be associated with obesity in Italy? Public Health Nutr 17:607–613
4. Feng R (2016) How much do we know about the heritability of BMI? Am J Clin Nutr 104:243–244
5. Labruna G, Pasanisi F, Fortunato G, Nardelli C, Finelli C, Farinaro E, Contaldo F, Sacchetti L (2011) Sequence analysis of the UCP1 gene in a severe obese population from Southern Italy. J Obes 2011:269043
6. Bracale R, Labruna G, Finelli C, Daniele A, Sacchetti L, Oriani G, Contaldo F, Pasanisi F (2012) The absence of polymorphisms in ADRB3, UCP1, PPARgamma, and ADIPOQ genes protects morbid obese patients toward insulin resistance. J Endocrinol Invest 35:2–4
7. Labruna G, Pasanisi F, Nardelli C, Tarantino G, Vitale DF, Bracale R, Finelli C, Genua MP, Contaldo F, Sacchetti L (2009) UCP1-3826 AG + GG genotypes, adiponectin, and leptin/adiponectin ratio in severe obesity. J Endocrinol Invest 32:525–529
8. Nardelli C, Labruna G, Liguori R, Mazzaccara C, Ferrigno M, Capobianco V, Pezzuti M, Castaldo G, Farinaro E, Contaldo F, Buono P, Sacchetti L, Pasanisi F (2013) Haplogroup T is an obesity risk factor: mitochondrial DNA haplotyping in a morbid obese population from southern Italy. Biomed Res Int 2013:631082
9. Brown CL, Perrin EM (2018) Obesity prevention and treatment in primary care. Acad Pediatr 18:736–745
10. Iaffaldano L, Nardelli C, Raia M, Mariotti E, Ferrigno M, Quaglia F, Labruna G, Capobianco V, Capone A, Maruotti GM, Pastore L, Di Noto R, Martinelli P, Sacchetti L, Del Vecchio L (2013) High aminopeptidase N/CD13 levels characterize human amniotic mesenchymal stem cells and drive their increased adipogenic potential in obese women. Stem Cells Dev 22:2287–2297
11. WHO (2018) http://www.who.int/en/news-room/fact-sheets/detail/physical-activity

12. Gerovasili V, Agaku IT, Vardavas CI, Filippidis FT (2015) Levels of physical activity among adults 18–64 years old in 28 European countries. Prev Med 81:87–91
13. Pillay JD, van der Ploeg HP, Kolbe-Alexander TL, Proper KI, van Stralen M, Tomaz SA, van Mechelen W, Lambert EV (2015) The association between daily steps and health, and the mediating role of body composition: a pedometer-based, cross-sectional study in an employed South African population. BMC Public Health 15:174
14. Scheers T, Philippaerts R, Lefevre J (2013) SenseWear-determined physical activity and sedentary behavior and metabolic syndrome. Med Sci Sports Exerc 45:481–489
15. Cho ER, Shin A, Kim J, Jee SH, Sung J (2009) Leisure-time physical activity is associated with a reduced risk for metabolic syndrome. Ann Epidemiol 19:784–792
16. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, Owen N (2008) Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 31:369–371
17. Lakka TA, Laaksonen DE, Lakka HM, Mannikko N, Niskanen LK, Rauramaa R, Salonen JT (2003) Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. Med Sci Sports Exerc 35:1279–1286
18. Dong SS, Zhang YJ, Chen YX, Yao S, Hao RH, Rong Y, Niu HM, Chen JB, Guo Y, Yang TL (2018) Comprehensive review and annotation of susceptibility SNPs associated with obesity-related traits. Obes Rev 19:917–930
19. Loos RJ (2018) The genetics of adiposity. Curr Opin Genet Dev 50:86–95
20. Goni L, García-Granero M, Milagro FI, Cuervo M, Martínez JA (2018) Phenotype and genotype predictors of BMI variability among European adults. Nutr Diabetes 8:27
21. Liguori R, Labruna G, Alfieri A, Martone D, Farinaro E, Contaldo F, Sacchetti L, Pasanisi F, Buono P (2014) The FTO gene polymorphism (rs9939609) is associated with metabolic syndrome in morbidly obese subjects from southern Italy. Mol Cell Probes 28:195–199
22. Drenowatz C, Jakicic JM, Blair SN, Hand GA (2015) Differences in correlates of energy balance in normal weight, overweight and obese adults. Obes Res Clin Pract 9:592–602
23. Kalantari N, Doaei S, Keshavarz-Mohammadi N, Gholamalizadeh M, Pazan N (2016) Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions. ARYA Atheroscler. 12(6):281–290
24. Bak A, Tsiami A, Greene C (2017) Methods of assessment of hydration status and their usefulness in detecting dehydration in the elderly. Curr Res Nutr Food Sci J 5(2):43–54
25. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735–2752
26. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, Tiribelli C (2006) The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 6:33
27. Santos-Lozano A, Hernández-Vicente A, Pérez-Isaac R, Santín-Medeiros F, Cristi-Montero C, Casajús JA, Garatachea N (2017) Is the SenseWear Armband accurate enough to quantify and estimate energy expenditure in healthy adults? Ann Transl Med 5(5):97
28. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS (2011) 2011 compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575–1581
29. Pettee Gabriel K, McClain JJ, Lee CD, Swan PD, Alvar BA, Mitros MR, Ainsworth BE (2009) Evaluation of physical activity measures used in middle-aged women. Med Sci Sports Exerc 41(7):1403–1412
30. Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA, Razquin C, Marti A, Heianza Y, Huang T et al (2016) FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ 354:i4707
31. Graff M, Scott RA, Justice AE, Young KL, Feitosa MF, Barata L, Winkler TW, Chu AY, Mahajan A, Hadley D et al (2017) Genome-wide physical activity interactions in adiposity—a meta-analysis of 200,452 adults. PLoS Genet 13:e1006528
32. Kilpelainen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, Ahmad T, Mora S, Kaakinen M, Sandholt CH et al (2011) Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med 8:e1001116
33. Leonska-Duniec A, Ahmetov II, Zmijewski P (2016) Genetic variants influencing effectiveness of exercise training programmes in obesity—an overview of human studies. Biol Sport 33:207–214
34. Li S, Zhao JH, Luan J, Ekelund U, Luben RN, Khaw KT, Wareham NJ, Loos RJ (2010) Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. PLoS Med 7:e1000332
35. Vimaleswaran KS, Li S, Zhao JH, Luan J, Bingham SA, Khaw KT, Ekelund U, Wareham NJ, Loos RJ (2009) Physical activity attenuates the body mass index-increasing influence of genetic variation in the FTO gene. Am J Clin Nutr 90:425–428
36. Myers A, Gibbons C, Finlayson G, Blundell J (2017) Associations among sedentary and active behaviours, body fat and appetite dysregulation: investigating the myth of physical inactivity and obesity. Br J Sports Med 51:1540–1544
37. Utz-Melere M, Targa-Ferreira C, Lessa-Horta B, Epifanio M, Mouzaki M, Mattos AA (2018) Non-alcoholic fatty liver disease in children and adolescents: lifestyle change—a systematic review and meta-analysis. Ann Hepatol 17:345–354
38. Labruna G, Pasanisi F, Nardelli C, Caso R, Vitale DF, Contaldo F, Sacchetti L (2011) High leptin/adiponectin ratio and serum triglycerides are associated with an "at-risk" phenotype in young severely obese patients. Obesity (Silver Spring) 19:1492–1496
39. Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Manas LR, Mattace Raso FU, Muiesan ML, Ryliskyte L, Rietzschel E, Strait J, Vlachopoulos C, Volzke H, Lakatta EG, Nilsson PM (2015) Metabolic syndrome across Europe: different clusters of risk factors. Eur J Prev Cardiol 22:486–491
40. Siervo M, Lara J, Celis-Morales C, Vacca M, Oggioni C, Battezzati A, Leone A, Tagliabue A, Spadafranca A, Bertoli S (2016) Age-related changes in basal substrate oxidation and visceral adiposity and their association with metabolic syndrome. Eur J Nutr 55:1755–1767
41. Valerio G, Maffeis C, Zucchini S, Lombardo F, Toni S, Rabbone I, Federico G, Scaramuzza A, Franzese A, Cherubini V, Zedda MA, Calcaterra V, Lera R, Cardinale G, Bruzzese M, Iughetti L, Gallo F, De Donno V, De Berardinis F, Iafusco D (2014) Geographic variation in the frequency of abdominal adiposity and metabolic syndrome in Italian adolescents with type 1 diabetes. Acta Diabetol 51:163–165
42. Caserta CA, Mele A, Surace P, Ferrigno L, Amante A, Messineo A, Vacalebre C, Amato F, Baldassarre D, Amato M, Marcucci F, Zuin M (2017) Association of non-alcoholic fatty liver disease and cardiometabolic risk factors with early atherosclerosis in an adult population in Southern Italy. Ann Ist Super Sanita 53:77–81

43. Visram S, Clarke C, White M (2014) Making and maintaining lifestyle changes with the support of a lay health advisor: longitudinal qualitative study of health trainer services in northern England. PLoS ONE 9:e94749
44. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS, Clausen JO, Sandbaek A, Lauritzen T, Hansen L, Jørgensen T, Pedersen O, Hansen T (2008) Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. Diabetes 57(1):95–101
45. Ruiz JR, Labayen I, Ortega FB, Legry V, Moreno LA, Dallongeville J et al (2010) Attenuation of the effect of the FTO rs9939609 polymorphism on total and central body fat by physical activity in adolescents: the HELENA study. Arch Pediatr Adolesc Med 164(4):328–333
46. Akbari ME, Gholamalizadeh M, Doaei S, Mirsafa F (2018) FTO gene affects obesity and breast cancer through similar mechanisms: a new insight into the molecular therapeutic targets. Nutr Cancer 70(1):30–36
47. Papadimitriou A, Nicolaidou P, Fretzayas A, Chrousos GP (2010) Clinical review: constitutional advancement of growth, a.k.a. early growth acceleration, predicts early puberty and childhood obesity. J Clin Endocrinol Metab 95:4535–4541
48. Scheers T, Philippaerts R, Lefevre J (2012) Assessment of physical activity and inactivity in multiple domains of daily life: a comparison between a computerized questionnaire and the SenseWear Armband complemented with an electronic diary. Int J Behav Nutr Phys Act 9:71
49. Scheers T, Philippaerts R, Lefevre J (2012) Variability in physical activity patterns as measured by the SenseWear Armband: how many days are needed? Eur J Appl Physiol 112:1653–1662

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.