J Physiol Biochem (2016) 72:169–181
DOI 10.1007/s13105-016-0467-7

ORIGINAL PAPER

Maternal and neonatal *FTO* rs9939609 polymorphism affect insulin sensitivity markers and lipoprotein profile at birth in appropriate-for-gestational-age term neonates

Eva Gesteiro · Francisco J. Sánchez-Muniz · Carolina Ortega-Azorín · Marisa Guillén · Dolores Corella · Sara Bastida

Received: 11 November 2015 / Accepted: 27 January 2016 / Published online: 6 February 2016

Abstract The influence of maternal fat mass and obesity (*FTO*) gene polymorphism on neonatal insulin sensitivity/resistance biomarkers and lipoprotein profile has not been tested. The study aimed to assess the association between the *FTO* rs9939609 polymorphism in mother-neonate couples and neonatal anthropometrical measurements, insulin sensitivity/resistance, and lipid and lipoprotein concentrations at birth. Fifty-three term, appropriate-for-gestational-age, Caucasian newborns together with their respective mothers participated in a cross-sectional study. Sixty-six percent of mothers and neonates carried the A allele (being AA or AT). TT mothers gained less weight during pregnancy, but non-significant maternal gene influence was found for neonatal bodyweight, body mass index, or ponderal index. Neonates from AA + AT mothers showed lower glucose, insulin, and homeostatic model assessment insulin resistance (HOMA-IR) but higher homeostatic model assessment insulin sensitivity (HOMA-IS) and homocysteine than neonates whose mothers were TT. AA + AT neonates had higher insulin and HOMA-IR than TT. The genotype neonatal × maternal association was tested in the following four groups of neonates: TT neonates × TT mothers (nTT × mTT), TT neonates × AA + AT mothers (nTT × mAA + AT), AA + AT neonates × TT mothers (nAA + AT × mTT), and AA + AT neonates × AA + AT mothers (nAA + AT × mAA + AT). Non-significant interactions between neonatal and maternal alleles were found for any parameter tested. However, maternal alleles affected significantly glucose, insulin, HOMA-IR, and homocysteine while neonatal alleles the arylesterase activity. Most significant differences were found between nATT + AA × mTT and nATT + AA × mAA + AT. Glycemia, insulinemia, and HOMA-IR were lower, while the Mediterranean diet adherence (MDA) was higher in the mAA + AT vs. mTT whose children were AA + AT. This dietary fact seems to counterbalance the potential negative effect on glucose homeostasis of the obesogenic A allele in neonates.

Keywords Appropriate-for-gestational-age · *FTO* gene · Healthy eating index · Insulin sensitivity · Lipoproteins · Mediterranean diet adherence · Term neonates

Abbreviations

AE	Arylesterase
AGA	Appropriate for gestational age
Apo	Apolipoprotein
BMI	Body mass index
CVD	Cardiovascular disease

E. Gesteiro · F. J. Sánchez-Muniz (✉) · S. Bastida
Departamento de Nutrición y Bromatología I (Nutrición), Facultad de Farmacia, Universidad Complutense de Madrid, Plaza Ramón y Cajal s/n, 28040 Madrid, Spain
e-mail: frasan@ucm.es

E. Gesteiro
Servicio de Análisis Clínicos, Hospital de Mérida, Polígono Nueva Ciudad s/n, 06800 Mérida (Badajoz), Spain

C. Ortega-Azorín · M. Guillén · D. Corella
Departamento de Medicina Preventiva y CIBER Fisiopatología de la Obesidad y Nutrición, ISCIII, Facultad de Medicina, Universidad de Valencia, 46010 Valencia, Spain

FTO	Fat mass and obesity-associated gene
GDM	Gestational diabetes
HDLc	Cholesterol transported by high-density lipoproteins
HEI	Healthy eating index
HOMA-IR	Homeostatic model assessment insulin resistance
HOMA-IS	Homeostatic model assessment insulin sensitivity
IR	Insulin resistance
LDLc	Cholesterol transported by low-density lipoproteins
oxLDL	Oxidized LDL
mAA + AT	Mothers carrying the *FTO* rs9939609 A allele
MDA	Mediterranean diet adherence
MS	Metabolic syndrome
mTT	Mothers homozygous for the *FTO* rs9939609 T allele
nAA + AT	Neonates carrying the *FTO* rs9939609 A allele
nTT	Neonates homozygous for the *FTO* rs9939609 T allele
PI	Ponderal index
QUICKI	Quantitative insulin sensitivity check index
SNP	Single-nucleotide polymorphism
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
tHcys	Homocysteine
TG	Triglycerides

Introduction

Insulin resistance (IR) has been suggested to have a fetal programming [4]. The fat mass and obesity (*FTO*)-associated gene is located on 16q12.2. The rs9939609 *FTO* (T ≥ A) has been associated with body mass index (BMI) increasing weight of A-homozygous adults about 3 kg. *FTO* association with increased risk of childhood obesity was also demonstrated by Frayling et al. [11], although the effects were observed at age seven. The *FTO* expression is especially high in the hypothalamus, suggesting its involvement in the energetic balance [42]. The risk alleles have been associated with poorer eating behaviors [9, 11, 39]; higher food, energy, and fat intakes; and specific preference for energy-dense foods with high-fat content [20, 36]. In vitro experiments suggest that *FTO* exert gene regulation at RNA levels in humans [13, 23, 24]. Its role in energy homeostasis is supported by some studies showing that *FTO* mRNA expression is regulated by food intake [12, 13, 41, 42], glycemia [35], weight status [43, 44], and energy expenditure [3, 10, 41].

Harbron et al. [19] investigated the association of *FTO* polymorphisms (rs1421085 and rs15817449) and food intake, eating behavior, and changes in BMI in adults with BMI ≥27 kg/m^2. The risk alleles were associated with higher hunger and emotional disinhibition scores and with higher intakes of high-fat foods and refined starch. Ortega-Azorín et al. [34] reported that the association of the *FTO* rs9939609 polymorphism with type 2 diabetes (T2DM) is highly modulated by diet in subjects presenting low adherence to the Mediterranean diet (MDA) pattern.

High-quality diets during pregnancy have been recommended to assure a correct embryo and fetal growth and functionality [38]. Thus, diets with high score for healthy eating index (HEI) or MDA followed during pregnancy decrease the risk of both high insulin and homeostatic model assessment insulin resistance (HOMA-IR) at birth [15]. In addition, neonates from mothers that followed high-score MDA diets during pregnancy showed less cholesterol transported by LDL (LDLc), apolipoprotein (Apo) B, and homocysteine (tHcys) but higher ApoA1/ApoB ratio than neonates whose mothers followed low MDA score diets [17].

Higher IR and preference for hypercaloric diets have been described in the A carriers [36]. Information about the effects of *FTO* polymorphism on glucose and insulin levels in term neonates is scarce [29]. To the best of our knowledge, this is the first study associating neonatal and maternal *FTO* polymorphisms and lipid profile and tHcys at birth. Moreover, the effect of this polymorphism on glucose and insulin levels at birth in appropriate-for-gestational-age (AGA) term neonates has never been tested.

Present paper hypothesizes that maternal and neonatal *FTO* polymorphisms affect neonatal parameters related to metabolic syndrome (MS). The aims of this paper were (a) to find out the effects of neonatal and maternal *FTO* rs9939609 polymorphism on different parameters related to IR, tHcys, lipid, and lipoprotein levels at birth; (b) the possible associations between the

maternal and neonatal *FTO* polymorphism on those parameters; and (c) the possible modulating effect of the maternal diet quality during pregnancy on these parameters.

Methods and materials

Subjects

It is a cross-sectional study performed in the Mérida Hospital (Spain), in accordance with the Helsinki Declaration and approved by the Management and Ethical Committee of the Mérida Hospital. Permission for DNA genotyping was obtained from 65 participating mothers. All selected neonates were Caucasian, singleton, full-term (born between weeks 37 and <42), normoweight (between 2.5 and <4.0 kg), AGA (weight ≥ percentile 10 for its gestational age), and born without fetal distress, by eutocic delivery with cephalic presentation from mothers without gestational diabetes (GDM). Thus, 53 mother-neonate couples were finally selected according to the inclusion criteria. The participation rate was about 24 % of participating women in the Mérida cohort study [16]. Nutritional information during pregnancy was available in 30 mothers.

Protocol

Data related to the delivery, mothers' age, and neonatal characteristics were obtained from hospital records. Anthropometrical measurements were performed by trained personnel. After delivery, in order to avoid any contamination with maternal DNA (blood and efflux), cord blood was obtained by arterial puncture and collected in BD Vacutainer® SST II tubes containing separation gel (Becton Dickinson, Plymouth, UK). Serum was obtained by blood centrifugation (3500 rpm, 5 min), and aliquots were stored at −18 °C until processing.

Between weeks 24 and 28 of pregnancy, future mothers were screened for GDM using the O'Sullivan glucose tolerance test [33]. Shortly, pregnant women received 50 g of glucose and after 1 h were tested for glycemia. They were considered to have impaired glucose tolerance when glycemia was over 140 mg/dL (≥7.78 mmol/L). When mothers were diagnosed of impaired glucose tolerance, a second test was done. They received 100 g of glucose and were tested after 1, 2, and 3 h for GDM.

Assays

Genomic DNA was isolated from whole blood. The rs9939609 *FTO* single-nucleotide polymorphism (SNP) was determined using a 7900HT sequence detection system (Applied Biosystems by Life Technologies, Foster City, CA, USA) and a fluorescent allelic discrimination TaqMan™ assay by standard procedures. For quality control purposes, 10 % of randomly selected samples were genotyped a second time, and there were no discrepancies. The calling rate was 95 %. Genotype frequencies did not deviate from Hardy-Weinberg equilibrium expectation ($P > 0.1$). Similarly to other Mediterranean populations, about two third of participating mothers and neonates were AA + AT [5].

Four genotype neonatal × maternal allele associations were tested: (a) neonates homozygous for the *FTO* rs9939609 T allele × mothers homozygous for the *FTO* rs9939609 T allele (nTT × mTT), (b) neonates homozygous for the *FTO* rs9939609 T allele × mothers carrying the *FTO* rs9939609 A allele (nTT × mAA + AT), (c) neonates carrying the *FTO* rs9939609 A allele × mothers homozygous for the *FTO* rs9939609 T allele (nAA + AT × mTT), and (d) neonates carrying the *FTO* rs9939609 A allele × mothers carrying the *FTO* rs9939609 A allele (nAA + AT × mAA + AT).

Serum glucose concentrations were measured by the glucose hexokinase method (Gluco-quant®), total cholesterol (TC) by the colorimetric enzymatic method (CHOD-PAP), cholesterol transported by high-density lipoproteins (HDLc) by the homogeneous enzymatic method (HDL plus second generation), triglycerides (TG) by the colorimetric enzymatic method (GPO-PAP), and ApoA1 and ApoB by the immunoturbidimetric method (Tina-quant®). All of them were supplied by Roche Diagnostics (Basel, Switzerland) and processed in a Roche/Hitachi Modular P (Roche Diagnostics, Basel, Switzerland) analyzer. LDLc was calculated using the formula of Friedewald et al. as validated in neonates by Glueck et al. [18]. Insulin concentrations were determined by electrochemiluminescence immunoassay (ECLIA) supplied by Roche Diagnostics in a Roche/Hitachi Modular Analytics E 170 analyzer (Roche Diagnostics, Basel, Switzerland). tHcys was measured by fluorescence polarization immunoassay (FPIA) supplied by Abbott in

an IMX® System analyzer (Abbott Diagnostics, IL, USA). Arylesterase (AE) activity was measured according to Nus et al. method [32] at 37 °C. One unit of AE was defined as the millimole of phenol formed from phenyl acetate per minute monitorized using a thermostated T80+ spectrophotometer (PG Instruments® Ltd., Wibtoft, Leics, UK). Oxidized LDL (oxLDL) was determined by an ELISA test kit from Mercodia Laboratories (Upsala, Sweden) using an ELx808 BioTek® spectrophotometer (BioTek Instruments, Winoosky, VT, USA).

Our laboratory participates in the Spanish Clinical Chemistry Society (SEQC) External Quality Evaluation Program, which follows UNE-EN-ISO 9001:2000 standards and is certified by AENOR. All the assays were properly calibrated and performed under internal and external quality control provided by the manufacturers and SEQC, respectively. Intra-assay and inter-assay variation coefficients were 1 and 1.7 % for glucose, 1.5 and 4.9 % for insulin, 0.8 and 1.7 % for TC, 1.5 and 1.8 % for TG, 0.9 and 1.85 % for HDLc, 1 and 2.4 % for ApoA1, 1.5 and 2.5 % for ApoB, 2.3 and 2.8 % for tHcys, 8 and 8.9 % for AE, and 4.5 and 5.0 % for oxLDL, respectively.

The indices used to test IR or insulin sensitivity were the quantitative insulin sensitivity check index (QUICKI), HOMA-IR, homeostatic model assessment insulin sensitivity (HOMA-IS), and the glucose/insulin ratio [15].

P_{25} and P_{75} described in the Mérida study reference population for some components of the MS [14, 16] were used in this study as cutoff point to set the percentage of neonates from AA + AT and TT mothers with low and high values, respectively.

Dietary data collection

Details of dietary collection and managements have been already published [17]. Briefly, participants, guided by a trained dietician, completed a food frequency questionnaire that included 169 items classified according to food groups and based on questionnaires used and validated previously. Photographs of sample portions were used to estimate the serving size and volumes consumed. The dietician reviewed, together with the volunteer, the usual consumption frequency of each food (per day/week/month), together with the normal food helping size. Information about different food group consumption (oils and fats, vegetables, fruits, legumes, cereals, fish, meat and eggs, sweets and bakery, nuts, poultry, and dairy products), and dietary habits was also obtained during pregnancy.

HEI and MDA, used as global dietary quality indices, were evaluated in 30 mothers following criteria stated in a previous paper, where cutoff points for HEI and MDA were set at 70 and 7, respectively [15]. The test for evaluating MDA was an adaptation to 13-point scale of the one used in the PREDIMED study (acronym of "Efectos de la dieta mediterránea en la prevención primaria de la enfermedad cardiovascular"), after considering that alcohol should not be consumed during pregnancy as indicated in [15]. From the 30 mothers evaluated, 10 were TT while 20 were AA + AT. Nine of their neonates were TT while 21 were AA + AT. Attending to the neonatal × maternal *FTO* association, 5 were nTT × mTT, 4 nTT × mAA + AT, 5 nAA + AT × mTT, and 16 nAA + AT × mAA + AT.

Statistics

The Z Kolmogorov-Smirnov test was used for testing the normal data distribution. IR markers and TG were normalized by natural log transformation. To avoid any potential effects of maternal glycemia on neonatal parameters, glycemia at O'Sullivan test was used as covariate for data adjusting. Neonatal insulin and TC were considered major outcomes. Taken into account allele prevalence of rs9939609 *FTO* in Mediterranean populations [34], this study showed a power at least of 85 % (nominal alpha = 0.05) to detect mean differences between A allele carrier and TT neonate groups of 12 mg/dL for TC and 3 mIU/L for insulin. The interaction between maternal and neonatal *FTO* polymorphisms was tested in the following four groups: nTT × mTT, nTT × mAA + AT, nAA + AT × mTT, and nAA + AT × mAA + AT by two factorial (mother and neonatal allele effects) univariate ANOVA. Differences between the nTT × mTT and nTT × mAA + AT, nAA + AT × mTT and nAA + AT × mAA + AT, nTT × mTT and nAA + AT × mTT, and nTT × mAA + AT and nAA + AT × mAA + AT associations were tested by the unpaired *t* test. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the SPSS (version 22.0) and SAS (version 12.3) statistical software packages.

Results

Anthropometrical and biochemical data of selected neonates and their respective mothers did not significantly differ from AGA-neonate sample of the Mérida study (data not shown). Eighteen mothers were T homozygous and 35 were AA + AT, while 17 neonates were T homozygous and 36 were AA + AT.

Table 1 shows some anthropometrical, analytical, and dietary characteristics of the studied mothers. Weight gain during pregnancy was significantly higher in mAA + AT ($P = 0.038$). mTT showed significantly lower MDA score diet ($P = 0.006$) but non-significantly higher HEI scores. Mothers of nAA + AT and nTT showed equivalent age, pregnancy weight gain, and diet quality scores.

The anthropometrical and clinical characteristics of the group of 30 mTT and mAA + AT (and their respective children) whose nutrition data were available did not significantly differ from those of the whole group of 53 mother-neonate couples studied in the present paper.

Table 2 shows the effects of maternal and neonatal *FTO* polymorphisms on the neonatal anthropometry and IR markers. Offspring of mAA + AT presented lower glucose ($P = 0.015$), insulin ($P = 0.049$), and HOMA-IR ($P = 0.015$) but higher HOMA-IS ($P = 0.015$) at birth than that of mTT. However, nAA + AT had higher insulin ($P = 0.048$) and HOMA-IR ($P = 0.035$) than their T homozygous counterparts.

Table 3 shows the effect of maternal and neonatal *FTO* polymorphisms on neonatal tHcys, lipids, and lipoproteins. Only tHcys ($P = 0.029$) was affected by the maternal *FTO* polymorphism. Neonates born from mAA + AT showed higher tHcys levels than those from mTT. Considering the neonatal *FTO* polymorphism, nAA + AT showed marginally significant lower ($P = 0.058$) TG levels than their TT counterparts.

Figure 1 shows the percentage of neonates from mAA + AT and mTT presenting values that lay below P_{25} or above P_{75} described in the Mérida study reference population for some components of the MS [14, 16]. Lower levels of MS markers were more prevalent in neonates from mAA + AT.

Table 4 shows the effect of the *FTO* neonate × mother allele interaction on the different parameters tested. Only significant results are shown. None of the parameters tested were significantly affected by the neonate × mother allele factor interaction. Maternal allele significantly affected pregnancy weight gain, neonatal glycemia, insulinemia, HOMA-IR, HOMA-IS, the glucose/insulin ratio, and homocysteinemia (at least $P < 0.05$), while neonatal allele affected AE activity. Lower levels of glucose, insulin, AE, and HOMA-IR (all $P < 0.05$) but higher ($P < 0.05$) pregnancy weight gain and the HOMA-IS were found in nAA + AT × mAA + AT vs. nAA + AT × mTT. Higher AE activity ($P < 0.05$) was found in nAA + AT × nTT vs. nTT × mTT.

Figure 2 shows that mothers' diet in the nAA + AT × mTT interaction group had significantly lower MDA score ($P = 0.05$) than those in the nAA + AT × mAA + AT group. The anthropometrical and clinical characteristics of the 30 mothers (and that of their respective children) distributed in the four association groups where nutrition data were available did not significantly differ from those of the 53 neonate-mother couples distributed in the four groups and tested for all other parameters (data not shown).

Discussion

Present most relevant results show that newborns from mAA + AT have lower insulin and HOMA-IR than their TT counterparts, while opposite results were found in nAA + AT. A higher percentage of neonates under the P_{25} level assessed by Gesteiro et al. [14] for some MS components were delivered by mAA + AT.

In agreement with previous studies [11, 25, 26, 34], no significant associations between the maternal or neonatal *FTO* rs9939609 polymorphism and birthweight, height, BMI, or ponderal index (PI) at birth were found. Several research groups tried to find when the *FTO* effect on BMI begins. Frayling et al. [11] reported that rs9939609 polymorphism was associated with changes in BMI and obesity at age 7. Da Silva et al. [7] observed significant differences in BMI and energy intake from lipids at 4 years old. Rzehak et al. [37] found no association of *FTO* variants with birthweight but could show that significant association developed over time in their population at age 4. López Bermejo et al. [29] assessed that at age of 2 weeks, some differences in PI, weight, and body fat composition associated to the *FTO* polymorphism were observed.

mAA + AT had 6.9 % higher pre-pregnancy weight and gained 18.8 % more weight during pregnancy than their T-homozygous counterparts. Similar results on pregnant A carriers have been observed by Lawlor et al. [26]. *FTO* polymorphisms have been associated

Table 1 Maternal age, pregnancy weight gain, serum glucose and cholesterol, health eating index (HEI), and Mediterranean diet adherence (MDA) score of the studied population depending on the maternal and neonatal *FTO* rs9939609 polymorphism

Parameters	Maternal *FTO*	Number	Values	ANOVA (*P*)	Neonatal *FTO*	Number	Values	ANOVA (*P*)
Mother's age (years)	TT	18	30.3 ± 7.5 (26.7–33.9)	0.42	TT	17	32.1 ± 4.6 (29.8–34.3)	0.085
	AA + AT	35	29.1 ± 4.4 (27.6–30.6)		AA + AT	36	28.4 ± 5.4 (26.6–30.2)	
Pregnancy weight gain (kg)	TT	18	10.1 ± 2.3 (8.9–11.3)	0.038	TT	17	10.4 ± 2.1 (9.2–11.6)	0.094
	AA + AT	35	12.0 ± 3.2 (10.8–13.1)		AA + AT	36	11.9 ± 0.7 (10.6–13.3)	
Mother glucose (mg/dL)	TT	18	84.2 ± 7.1 (80.8–87.6)	0.44	TT	17	82.6 ± 4.1 (80.6–84.6)	0.34
	AA + AT	35	82.9 ± 5.5 (81.0–84.8)		AA + AT	36	83.5 ± 6.5 (81.3–85.7)	
Mother cholesterol (mg/dL)	TT	18	222.6 ± 32.6 (207.0–238.1)	0.13	TT	17	235.6 ± 37.5 (217.2–253.9)	0.60
	AA + AT	35	249.2 ± 50.9 (231.9–266.6)		AA + AT	36	242.9 ± 50.6 (225.9–260.0)	
HEI[a]	TT	10	72.8 ± 9.8 (65.7–79.8)	0.21	TT	9	74.3 ± 10.0 (66.6–82.0)	0.29
	AA + AT	20	67.8 ± 10.2 (63.0–72.5		AA + AT	21	69.9 ± 10.4 (65.1–74.6)	
MDA[b]	TT	10	5.9 ± 0.8 (5.4–6.5)	0.006	TT	9	7.0 ± 1.2 (6.1–8.0)	0.29
	AA + AT	20	7.0 ± 1.1 (6.5–7.6)		AA + AT	21	6.6 ± 1.0 (6.1–7.0)	
Negative/positive O'Sullivan test[c]	TT	12/6		0.23[c]	TT	10/7		0.53[c]
	AA + AT	28/7			AA + AT	26/10		

Values are mean ± SD (95 % CI) once adjusted for maternal glycaemia at the O'Sullivan test

N sample size

[a] HEI, 100-point scale

[b] MDA, 13-point scale

[c] Chi-squared test

Table 2 Neonatal anthropometrical parameters, glucose, and insulin resistance/sensitivity markers of the studied population at birth depending on the maternal and neonatal *FTO* rs9939609 polymorphism

Neonatal parameters	Maternal *FTO*	Number	Values	ANOVA (*P*)	Neonatal *FTO*	Number	Values	ANOVA (*P*)
Gestational age (weeks)	TT	18	39.8 ± 1.3 (39.1–40.4)	0.44	TT	17	39.2 ± 1.3 (38.55–39.79)	0.14
	AA + AT	35	39.5 ± 0.95 (39.2–39.8)		AA + AT	36	39.7 ± 0.9 (39.38–40.00)	
Neonatal weight (kg)	TT	18	3.4 ± 0.3 (3.3–3.5)	0.95	TT	17	3.3 ± 0.3 (3.18–3.49)	0.30
	AA + AT	35	3.4 ± 0.3 (3.3–3.5)		AA + AT	36	3.4 ± 0.3 (3.3–3.5)	
Neonatal BMI (kg/m^2)	TT	18	13.9 ± 1.0 (13.5–14.4)	0.38	TT	17	13.6 ± 1.0 (13.1–14.1)	0.57
	AA + AT	35	13.6 ± 1.1 (13.3–14.0)		AA + AT	36	13.8 ± 1.1 (13.4–14.1)	
Neonatal PI (kg/m^3)	TT	18	28.2 ± 2.7 (27.0–29.5)	0.21	TT	17	27.4 ± 2.8 (26.1–28.8)	0.86
	AA + AT	35	27.2 ± 2.3 (26.4–28.0)		AA + AT	36	27.5 ± 2.3 (26.7–28.3)	
Glucose (mg/dL)	TT	18	84.3 ± 31.8 (69.2–99.5)	0.015	TT	17	73.3 ± 11.4 (67.7–78.8)	0.70
	AA + AT	35	65.417.0 (57.6–71.3)		AA + AT	36	69.6 ± 26.4 (60.7–78.5)	
Insulin (mIU/L)	TT	18	7.1 ± 5.4 (4.5–9.7)	0.049	TT	17	3.5 ± 1.8 (2.6–4.3)	0.048
	AA + AT	35	4.3 ± 3.1 (3.7–4.8)		AA + AT	36	5.6 ± 4.4 (4.2–7.2)	
Glucose/insulin	TT	18	19.1 ± 10.4 (14.1–24.0)	0.24	TT	17	31.4 ± 20.3 (21.5–41.3)	0.11
	AA + AT	35	26.5 ± 20.2 (19.6–33.4)		AA + AT	36	21.9 ± 17.1 (16.14–27.6)	
HOMA-IR	TT	18	1.7 ± 2.0 (0.7–2.6)	0.015	TT	17	0.6 ± 0.3 (0.47–0.77)	0.035
	AA + AT	35	0.7 ± 0.5 (0.5–0.9)		AA + AT	36	1.1 ± 1.0 (0.73–1.41)	
HOMA-IS	TT	18	1.4 ± 1.1 (0.9–2.0)	0.015	TT	17	2.6 ± 1.9 (1.6–3.5)	0.68
	AA + AT	35	2.9 ± 2.5 (2.0–3.7)		AA + AT	36	2.5 ± 2.4 (1.7–3.3)	
QUICKI	TT	18	0.4 ± 0.1 (0.4–0.5)	0.74	TT	17	0.4 ± 0.1 (0.4–0.5)	0.94
	AA + AT	35	0.42 ± 0.09 (0.4–0.5)		AA + AT	36	0.4 ± 0.1 (0.4–0.5)	

Values are mean ± SD (95 % CI) once adjusted for maternal glycemia at the O'Sullivan test

PI ponderal index, *HOMA-IR and HOMA-IS* homeostasis model assessment insulin resistance and sensitivity, respectively, *QUICKI* quantitative insulin check index

Table 3 Lipids, lipoproteins, apolipoproteins, homocysteine, and arylesterase at birth depending on the maternal and neonatal *FTO* rs9939609 polymorphism

Neonatal parameters	Maternal *FTO*	Number	Values	ANOVA (*P*)	Neonatal *FTO*	Number	Values	ANOVA (*P*)
Triglycerides (mg/dL)	TT	18	36.3 ± 12.1 (30.6–42.1)	0.74	TT	17	43.8 ± 16.6 (35.6–51.9)	0.058
	AA + AT	35	34.8 ± 17.9 (28.7–40.9)		AA + AT	36	32.0 ± 15.4 (26.8–37.2)	
Total cholesterol (mg/dL)	TT	18	64.0 ± 15.0 (56.9–71.1)	0.46	TT	17	65.6 ± 11.0 (60.2–71.0)	0.23
	AA + AT	35	60.4 ± 14.2 (55.5–55.2)		AA + AT	36	59.8 ± 15.2 (54.6–64.9)	
HDLc (mg/dL)	TT	18	28.8 ± 9.2 (24.5–33.2)	0.31	TT	17	26.9 ± 5.6 (24.2–29.7)	0.82
	AA + AT	35	26.0 ± 7.6 (23.4–28.6)		AA + AT	36	26.7 ± 8.9 (23.7–29.7)	
LDLc (mg/dL)	TT	18	27.9 ± 8.3 (24.0–31.8)	0.75	TT	17	29.9 ± 6.4 (26.8–33.1)	0.22
	AA + AT	35	26.9 ± 9.6 (23.6–30.1)		AA + AT	36	26.1 ± 9.9 (22.7–29.4)	
OxLDL (mg/dL)	TT	18	45.6 ± 58.3 (17.9–73.3)	0.69	TT	17	29.4 ± 23.8 (17.7–41.1)	0.16
	AA + AT	35	48.9 ± 33.6 (37.4–60.3)		AA + AT	36	54.9 ± 43.9 (40.1–69.7)	
ApoA1 (mg/dL)	TT	18	76.5 ± 12.9 (70.3–82.6)	0.32	TT	17	77.9 ± 9.1 (73.4–82.3)	0.12
	AA + AT	35	72.1 ± 12.4 (67.9–76.3)		AA + AT	36	71.6 ± 13.4 (67.1–76.1)	
ApoB (mg/dL)	TT	18	30.0 ± 30.6 (15.4–44.5)	0.93	TT	17	36.9 ± 29.3 (22.5–51.2)	0.17
	AA + AT	35	29.5 ± 15.7 (23.4–35.5)		AA + AT	36	26.9 ± 15.7 (21.6–32.2)	
Homocysteine (μmol/L)	TT	18	4.8 ± 1.8 (4.0–5.7)	0.029	TT	17	5.5 ± 1.0 (5.1–6.0)	0.88
	AA + AT	35	5.9 ± 1.3 (5.5–6.4)		AA + AT	36	5.7 ± 1.7 (5.10–6.22)	
Arylesterase (U/L)	TT	18	34.4 ± 30.2 (20.0–48.8)	0.41	TT	17	17.3 ± 17.3 (8.8–25.8)	0.17
	AA + AT	35	25.8 ± 26.7 (16.7–34.9)		AA + AT	36	31.6 ± 29.6 (21.7–41.6)	

Values are mean ± SD (95 % CI) once adjusted for maternal glycemia at the O'Sullivan test

LDLc and HDLc cholesterol transported by LDL and HDL, respectively, *Apo* apolipoprotein, *oxLDL* oxidized LDL

with eating behavior and type of food consumed [9, 11, 19, 28, 42]. MDA and HEI scores tended to be lower and higher, respectively, in mTT than in mAA + AT. The former display a tendency for a higher consumption of animal foods and lower for some vegetables (data not shown), explaining the differences found in the quality of diets. As dietary information was not available in all the genotyped mothers, values have to be taken just as an approach. Nonetheless, according to a previous study [15], despite differences in mothers' MDA or HEI scores, neonates displayed similar bodyweight but their IR markers were highly affected by their mother's diet quality during pregnancy.

In adults, several studies have reported significant higher risk of T2DM in *FTO* A carriers [1, 6, 22]. Others have defined the association of *FTO* and obesity or MS

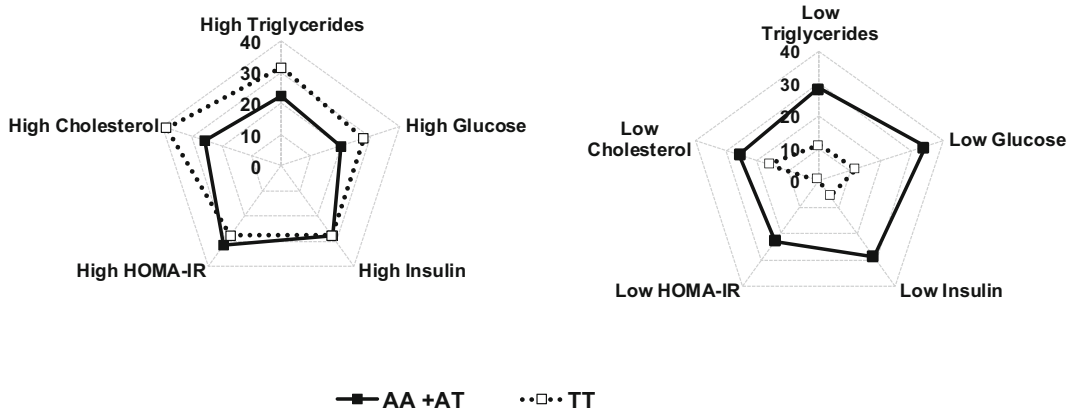

Fig. 1 Percentage of neonates whose mothers were genotyped for *FTO* rs9939609 as AA + AT or TT presenting high or low metabolic syndrome (MS) risk components. The percentile 25 for low levels and the percentile 75 for high levels stated by Gesteiro et al. [14, 16] were considered

Table 4 Pregnancy weight gain, neonatal glucose and insulin resistance/sensitivity markers, homocysteine, and arylesterase of the studied population depending on the neonatal and maternal *FTO* rs9939609 polymorphism interaction

	Neonate	Mother		ANOVA		
		TT	AA + AT	Neonatal allele	Maternal allele	Interaction
Pregnancy weight gain (kg)	TT	10.9 ± 1.8 (9.7–12.1)	12.3 ± 2.5 (10.6–14)	0.12	0.025	0.55
	AA + AT	9.6 ± 1.1b (8.9–10.3)	11.9 ± 2.2a (11.0–12.8)			
Glucose (mg/dL)	TT	93.8 ± 47.6 (74.7–112.9)	70.3 ± 13.0 (50.0–90.5)	0.39	0.016	0.86
	AA + AT	84.6 ± 37.6a (65.5–103.6)	64.2 ± 18.8b (53.2–75.2)			
Insulin (mIU/L)	TT	5.2 ± 4.2 (2.2–8.2)	3.6 ± 2.6 (0.5–6.8)	0.13	0.037	0.33
	AA + AT	8.7 ± 7.6a (5.8–11.7)	4.4 ± 3.5b (2.7–6.1)			
Glucose/insulin	TT	22.2 ± 9.1 (15.9–28.5)	33.7 ± 24.7 (14.4–52.0)	0.12	0.050	0.85
	AA + AT	14.8 ± 9.5b (8.5–21.1)	24.2 ± 13.7a (18.9–29.5)			
HOMA-IR	TT	1.5 ± 2.2 (0.6–2.4)	0.6 ± 0.5 (0.3–1.0)	0.48	0.012	0.58
	AA + AT	2.0 ± 2.1a (1.1–3.0)	0.7 ± 0.6b (0.2–1.2)			
HOMA-IS	TT	1.4 ± 0.7 (0.5–1.9)	3.0 ± 2.3 (1.4–4.6)	0.81	0.018	0.96
	AA + AT	1.3 ± 1.2b (0.5–2.1)	2.8 ± 2.4a (2.1–3.7)			
Homocysteine (μmol/L)	TT	5.2 ± 0.8 (4.2–6.1)	5.9 ± 0.8 (4.9–6.9)	0.98	0.047	0.74
	AA + AT	5.0 ± 1.7 (3.9–6.1)	6.0 ± 1.4 (5.5–6.6)			
Arylesterase (U/L)	TT	20.4 ± 14.9 (10.5–30.8)	19.8 ± 16.0 (8.5–31.1)	0.042	0.22	0.25
	AA + AT	47.3 ± 21.3a* (33.3–61.3)	27.4 ± 22.1b (18.9–35.9)			

Values are mean ± SD (95 % CI) of data where significant effects of neonatal or maternal alleles were found. Number of neonates in each group: nTT × mTT, $N = 9$; nTT × mAT + AA, $N = 8$; nAA + AT × mTT, $N = 9$; nAT + AA × mAT + AA, $N = 27$. Values in same row bearing different letters (a > b) were significantly different (unpaired Student's t test). For abbreviations, see text

*Values in same column were significantly different (unpaired Student's t test)

in different populations [2, 30].The association between the *FTO* rs9939609 polymorphism and T2DM in adults appears modulated by diet [34]. Thus, in A carriers, there was a high risk of T2DM when MDA was low even after adjustment for BMI, which did not appear when MDA was high [5, 34].

All participant mothers had equivalent fasting glycemia in pregnancy. The distribution of mothers being positive for the O'Sullivan test [33] was not significantly different in the nTT vs. nAA + AA groups or in the mTT vs. mAA + AT groups.

Mothers of both nTT and nAA + AT display similar HEI but significantly different MDA scores. Thus, MDA maternal diet quality seems to be determinant for differences in analytical data. As expected, neonates carrying the *obesogenic* A allele showed higher insulinemia and HOMA-IR than their TT counterparts [6, 22].

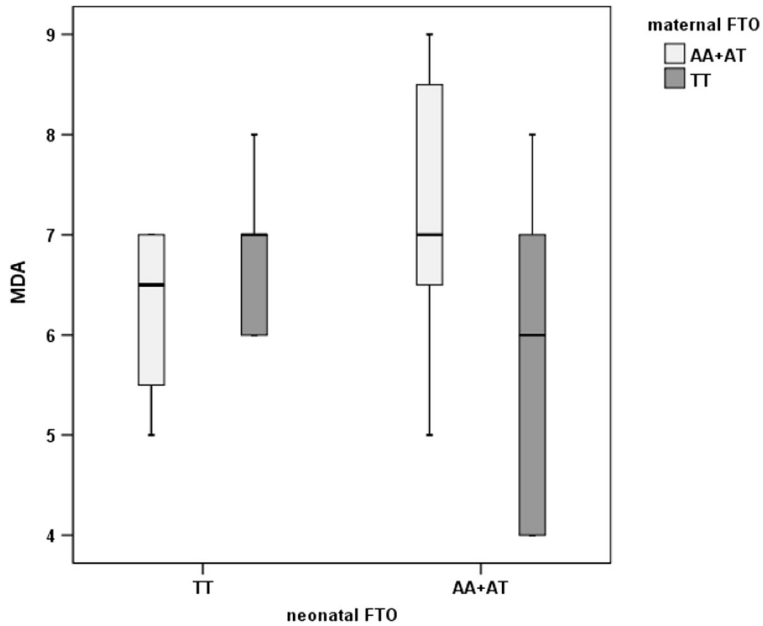

Fig. 2 Mediterranean diet adherence (MDA) in the four neonate groups (nTT × mTT, $N = 5$; nTT × mAA + AT, $N = 4$; nAA + AT × mTT, $N = 5$; and nAA + AT × mAA + AT, $N = 16$; for abbreviations, see text). MDA scores were significantly higher ($P = 0.05$) in the interaction of nAA + AT × mAA + AT than in the nAA + AT × mTT one

However, it seems controversial that newborns from mAA + AT had lower MS level components than their TT counterparts, as A carriers are more prone to develop obesity and T2DM in adulthood, thus to a higher-glucose homeostasis and lipid marker modification [6, 22]. Moreover, in 30–40 % of the neonates from mTT glucose, insulin and HOMA-IR were higher than the P_{75} reference value, while less than 10 % were lower than the P_{25} described by Gesteiro et al. [14]. In the case of AA + AT's offspring, between 20 and 40 % of neonates had values of these glucose homeostasis markers under the P_{25} of Gesteiro et al. (Fig. 1) [14]. In addition, mTT delivered more frequently neonates with high (>P_{75}) and less frequently neonates with low (<P_{25}) levels of MS markers than their AA + AT counterparts (Fig. 1).

Neonates from mAA + AT had higher tHcys levels than their TT counterparts, potentially related with the dysfunctional methylation suggested by Selhub [40]. It is known that *FTO* works as part of a complex process involving methylation and demethylation of nucleic acids [8, 23, 24]. These mAA + AT neonates had also significantly lower glucose, insulin, and HOMA-IR and higher HOMA-IS than their mTT counterparts. This was unexpected taking into account results in adults, showing that T homozygous vs. A carriers are less affected by BMI changes, obesity [11], and T2DM [21] and are less prone to develop cardiovascular disease (CVD) [27].

In contrast to the influence of maternal *FTO* on neonatal IR profile already discussed, nAA + AT showed increased insulin and HOMA-IR, suggesting that IR was already present in normoweights at birth. These findings concur with data for adults where A allele was associated to higher MS risk [2, 6, 45]. However, López Bermejo et al. [29] did not find any significant difference in glucose or insulin levels between the different *FTO* genotypes at birth. Although our study presents limitations due to the small sample size, it seems relevant the fact that belonging to mAA + AT offspring does not necessary imply suffering the negative effects attributed to the A allele. In fact, lower neonatal levels of glucose, insulin, AE, and HOMA-IR were found in the nAA + AT × mAA + AT group with respect to its nAA + AT × mTT counterpart (Table 4). Although those results seem difficult to be explained, they could be related to the higher MDA score of maternal diet found in the nAA + AT × mAA + AT group with respect to that of the nAA + AT × mTT one, suggesting that the benefits of the high MDA already indicated as mothers with higher MDA pregnancy diet deliver neonates with lower glucose, insulin, and HOMA-IR levels [17]. Western diets are rich in saturated fatty acids and poor in carbohydrates, dietary

factors related with the IR development [15, 31, 38]. Adequate weight gain during pregnancy plays a central role on glucose homeostasis at birth and should be adapted to pre-conception weights [38]. Mother pregnancy weight gain of all mothers scored in the range considered appropriate [38] (8.5 to 15 kg in our study). However, those mothers belonging to the nAA + AT × mAA + AT group gain the average weight gain and about 2.3 kg more weight than their nAA + AT × mTT counterparts, suggesting that higher MDA diet also contributes to weight gain and in turn to a better glucose homeostasis marker levels [17, 38]. Nonetheless, we are far from knowing major mechanisms involved in this neonatal × maternal genotype association. Moreover, we also do not know whether the association effects found at birth would be also present later in life in case of consuming diets similar to those followed during gestation by their respective mothers and should be checked in future follow-up study.

Although this study shows some limitations, (a) the low number of neonate × mother couples tested, (b) only SNP rs9939609 was studied, and (c) diet pattern was considered in 57 % of mothers, it has several strengths counterbalancing the mentioned limitations, (a) neonates were all AGA, normoweight, and strictly selected and their mothers did not suffer from GDM and had an adequate weight gain during pregnancy; (b) results were adjusted for maternal glycemia at the O'Sullivan test as confounder factor; and (c) it is the first study associating neonatal and maternal *FTO* polymorphisms with glucose homeostasis, lipid profile, and tHcys at birth.

Conclusion

Maternal *FTO* rs9939609 polymorphism affects in an opposite manner than neonatal *FTO* the IR and CVD markers in term, normoweight, AGA neonates at birth. Maternal *FTO* alleles affected much more than neonatal *FTO* alleles several parameters linked to the glucose homeostasis. The potential negative effects on glucose homeostasis observed in nAA + AT were counterbalanced in neonates delivered by mAA + AT but not by mTT, probably due to the higher MDA of their diets followed during pregnancy. Further investigations, replicating present associations in a larger population, are desirable to understand this interesting neonatal-maternal interaction.

Acknowledgments This study was supported by the Spanish AGL-2011 29644-C02-02 and CIBER 06/03/035 projects and the Research group of the UCM No. 920536. Thanks are due to the Gynecology and Obstetrics and Laboratory Services of Mérida Hospital (Spain), participant mothers and neonates, and Carmen Bravo from Departamento de Apoyo a la Investigación from the UCM. All authors have significantly contributed to the paper and agree with the present version of the manuscript. FJSM, the corresponding author and guarantor of the paper, has contributed to the study design, data discussion, and writing; EG to data acquisition, analysis, discussion, and writing of the paper; CO-A and MG to data acquisition and analysis; SB to the study design and data discussion; and DC contributed to data discussion and writing of the paper.

Compliance with ethical standards

Conflict of interest None.

References

1. Abbas S, Raza ST, Ahmed F, Ahmad A, Rizvi S, Mahdi F (2013) Association of genetic polymorphism of PPARγ-2, ACE, MTHFR, FABP-2 and FTO genes in risk prediction of T2DM. J Biomed Sci 20:80
2. Al-Attar SA, Pollex RL, Ban MR, Young TK, Bjerregaard P, Anand SS et al (2008) Association between the FTO rs9939609 polymorphism and the metabolic syndrome in a non-Caucasian multi-ethnic sample. Cardiovasc Diabetol 7:5
3. Arrizabalaga M, Larrarte E, Margareto J, Maldonado-Martín S, Barrenechea L, Labayen I (2014) Preliminary findings on the influence of FTO rs9939609 and MC4R rs17782313 polymorphisms on resting energy expenditure, leptin and thyrotropin levels in obese non-morbid premenopausal women. J Physiol Biochem 70:255–262
4. Barker DJP (1998) In utero programming of chronic disease. Clin Sci 95:115–128
5. Corella D, Carrasco P, Sorlí JV, Coltell O, Ortega-Azorín C, Guillén M et al (2012) Education modulates the association of the FTO rs9939609 polymorphism with body mass index and obesity risk in the Mediterranean population. Nutr Metab Cardiovasc Dis 22:651–658
6. Cruz M, Valladares-Salgado A, García-Mena J, Ross K, Edwards M, Ángeles-Martínez J et al (2010) Candidate gene association study conditioning on individual ancestry in patients with type 2 diabetes and metabolic syndrome from Mexico City. Diabetes Metab Res Rev 26:261–270
7. da Silva FC, Zandoná MR, Vitolo MR, Campagnolo PD, Rotta LN, Almeida S et al (2013) Association between a frequent variant of the FTO gene and anthropometric phenotypes in Brazilian children. BMC Med Genet 14:34

8. Davis W, van Rensburg SJ, Cronje FJ, Whati L, Fisher LR, van der Merwe L et al (2014) The fat and obesity associated FTO rs9939609 polymorphism is associated with elevated homocysteine levels in patients with multiple sclerosis screened for vascular risk factors. Metab Brain Dis 29:409–419
9. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P et al (2007) Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet 39:724–726
10. Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Brüning JC et al (2009) Inactivation of the FTO gene protects from obesity. Nature 458:894–988
11. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM et al (2007) A common variant in the FTO gene is associated with the body mass index and predisposes to childhood and adult obesity. Science 316:889–894
12. Fredriksson R, Hägglund M, Olszewski PK, Stephansson O, Jacobsson JA, Olszewska AM et al (2008) The obesity gene, FTO, is of ancient origin, upregulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. Endocrinology 149:2062–2071
13. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS et al (2007) The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 318:1469–1472
14. Gesteiro E, Bastida S, Sánchez-Muniz FJ (2009) Insulin resistance markers in term, normoweight neonates. The Merida cohort. Eur J Pediatr 168:281–288
15. Gesteiro E, Rodríguez-Bernal B, Bastida S, Sánchez-Muniz FJ (2012) Maternal diets with low healthy eating index or Mediterranean diet adherence scores are associated with high cord-blood insulin levels and insulin resistance markers at birth. Eur J Clin Nutr 66:1008–1015
16. Gesteiro E, Bastida S, Sánchez-Muniz FJ (2013) Cord-blood lipoproteins, homocysteine, insulin sensitivity/resistance marker profile, and concurrence of dysglycaemia and dyslipaemia in full-term neonates of the Mérida study. Eur J Pediatr 172:883–894
17. Gesteiro E, Bastida S, Rodríguez Bernal B, Sánchez-Muniz FJ (2015) Adherence to Mediterranean diet during pregnancy and serum lipid, lipoprotein and homocysteine concentrations at birth. Eur J Nutr 54:1191–1199
18. Glueck CJ, Steiner P, Leuba U (1973) Cord blood low-density lipoprotein-cholesterol estimation versus measurement with the preparative ultracentrifuge. J Lab Clin Med 82:467–472
19. Harbron J, van der Merwe L, Zaahl MG, Kotze MJ, Senekal M (2014) Fat mass and obesity-associated (FTO) gene polymorphisms are associated with physical activity, food intake, eating behaviors, psychological health, and modeled change in body mass index in overweight/obese Caucasian adults. Nutrients 6:3130–3152
20. Haupt A, Thamer C, Staiger H, Tschritter O, Kirchhoff K, Machicao F et al (2009) Variation in the FTO gene influences food intake but not energy expenditure. Exp Clin Endocrinol Diabetes 117:194–197
21. Hertel JK, Johansson S, Sonestedt E, Jonsson A, Lie RT, Platou CG et al (2011) FTO, type 2 diabetes, and weight gain throughout adult life: a meta analysis of 41,504 subjects from the Scandinavian HUNT, MDC and MPP studies. Diabetes 60:1637–1644
22. Horikoshi M, Hara K, Ito C, Shojima N, Nagai R, Ueki K et al (2007) Variations in the HHEX gene are associated with increased risk of type 2 diabetes in the Japanese population. Diabetologia 50:2461–2466
23. Jia G, Yang C, Yang S, Jian X, Yi C, Zhou Z et al (2008) Oxidative demethylation of 3-methylthymine and 3-methyluracil in single-stranded DNA and RNA by mouse and human FTO. FEBS Lett 582:3313–3319
24. Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y et al (2011) N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Chem Biol 7:885–887
25. Labayen I, Ruiz JR, Ortega FB, Gottrand F, Huybrechts I, Dallongeville J et al (2012) Body size at birth modifies the effect of fat mass and obesity associated (FTO) rs9939609 polymorphism on adiposity in adolescents: the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. Br J Nutr 107:1498–1504
26. Lawlor DA, Fraser A, Macdonald-Wallis C, Nelson SN, Palmer TM, Smith GD et al (2011) Maternal and offspring adiposity-related genetic variants and gestational weight gain. Am J Clin Nutr 94:149–155
27. Liu C, Mou S, Pan C (2013) The FTO gene rs9939609 polymorphism predicts risk of cardiovascular disease: a systematic review and meta-analysis. PLoS One 8:e71901
28. Livingstone KM, Celis-Morales C, Lara J, Ashor AW, Lovegrove JA, Martinez JA, Food4Me et al (2015) Associations between FTO genotype and total energy and macronutrient intake in adults: a systematic review and meta-analysis. Obes Rev 16:666–678
29. López Bermejo A, Petry CJ, Díaz M, Sebastiani G, de Zegher F, Dunger DB et al (2008) The association between the FTO gene and fat mass in humans develops by the postnatal age of two weeks. J Clin Endocrinol Metab 93:1501–1505
30. Moleres A, Rendo-Urteaga T, Zulet MA, Marcos A, Campoy C, Garagorri JM, EVASYON Study Group et al (2012) Obesity susceptibility loci on body mass index and weight loss in Spanish adolescents after a lifestyle intervention. J Pediatr 161:466–470
31. Nettleton JA, Jebb S, Risérus U, Koletzko B, Fleming J (2014) Role of dietary fats in the prevention and treatment of the metabolic syndrome. Ann Nutr Metab 64:167–178
32. Nus M, Sánchez-Muniz FJ, Sánchez-Montero JM (2006) A new method for the determination of arylesterase activity in human serum using simulated body fluid. Atherosclerosis 188:155–159
33. O'Sullivan BA, Henderson ST, Davis JM (1998) Gestational diabetes. J Am Pharm Assoc 38:364–371, quiz 372–373
34. Ortega-Azorín C, Sorlí JV, Asensio EM, Coltell O, Martínez-González MA, Salas Salvadó J et al (2012) Associations of the FTO rs9939609 and the MC4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the Mediterranean diet pattern is low. Cardiovasc Diabetol 11:137
35. Poritsanos NJ, Lew PS, Fischer J, Mobbs CV, Nagy JI, Wong D et al (2011) Impaired hypothalamic FTO expression in response to fasting and glucose in obese mice. Nutr Diabetes 1:e19
36. Rodríguez-López R, González-Carpio M, Serrano MV, Torres G, García de Cáceres MT, Herrera T et al (2010) Association of FTO gene polymorphisms and morbid obesity in the population of Extremadura (Spain). Endocrinol Nutr 57:203–209

37. Rzehak P, Scherag A, Grallert H, Sausenthaler S, Koletzko S, Bauer CP et al (2010) Associations between BMI and the FTO gene are age dependent: results from the GINI and LISA birth cohort studies up to age 6 years. Obes Facts 3:173–180
38. Sánchez-Muniz FJ, Gesteiro E, Espárrago Rodilla M, Rodríguez Bernal B, Bastida S (2013) Maternal nutrition during pregnancy conditions the fetal pancreas development, hormonal status and diabetes mellitus and metabolic syndrome biomarkers at birth. Nutr Hosp 28:250–274
39. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J et al (2007) Genome wide association scan shows genetic variants in the FTO gene are associated with obesity related traits. PLoS Genet 3:e115
40. Selhub J (1999) Homocysteine metabolism. Annu Rev Nutr 19:217–246
41. Stratigopoulos G, Padilla SL, LeDuc CA, Watson E, Hattersley AT, McCarthy MI et al (2008) Regulation of FTO/FTM gene expression in mice and humans. Am J Physiol Regul Integr Comp Physiol 294:R1185–R1196
42. Tung YC, Ayuso E, Shan X, Bosch F, O'Rahilli S, Coll AP et al (2010) Hypothalamic specific manipulation of FTO, the ortholog of the human obesity gene FTO, affects food intake in rats. PLoS One 5:e8771
43. Wåhlén K, Sjölin E, Hoffstedt J (2008) The common rs9939609 gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. J Lipid Res 49:607–611
44. Zabena C, González-Sánchez JL, Martínez-Larrad MT, Torres-García A, Álvarez-Fernández-Represa J, Corbatón-Anchuelo A et al (2009) The FTO obesity gene. Genotyping and gene expression analysis in morbidly obese patients. Obes Surg 19:87–95
45. Zhou D, Liu H, Zhou M, Wang S, Zhang J, Liao L et al (2012) Common variant (rs9939609) in the FTO gene is associated with metabolic syndrome. Mol Biol Rep 39:6555–6561