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Effect of the Ala12 Allele in the PPARγ-2 Gene on the Relationship Between Birth Weight and Body Composition in Adolescents: The AVENA Study

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ABSTRACT: The intent of this study was to assess whether the effect of birth weight on later body composition is modified by Pro12Pro, Pro12Ala, and Ala12Ala genotypes of the peroxisome proliferator–activated receptor γ-2 (PPARγ-2) gene. The PPARγ-2 gene polymorphism was genotyped in 273 adolescents aged 13–18.5 y, born at term and whose birth weight was known. They were selected from a cross-sectional multicenter study conducted in five Spanish cities in 2000–2002. Body mass index (BMI) was calculated from weight and height measurements, and body composition and fat distribution were estimated from skinfold thickness. A total of 229 subjects (111 males and 118 females) carried the Pro12Pro genotype and 44 (22 males and 22 females) the Pro12Ala and Ala12Ala PPARγ-2 genotypes. In the Pro12Pro group, birth weight *Z* score was positively associated with both fat-free mass (FFM) ($p < 0.05$) and fat mass (FM) ($p < 0.05$), but these relationships disappeared after controlling for age, gestational age, socioeconomic status (SES), physical activity, Tanner stage, sex, and BMI. In the Ala12 group, birth weight *Z* score was positively associated with FFM ($p < 0.01$), and this relationship remained significant after controlling for confounding variables ($p < 0.05$). Small body weight at birth may program lower FFM in adolescents carrying the Ala12 allele in the PPARγ-2 gene. **(*Pediatr Res* 62: 615–619, 2007)**

Numerous studies have observed associations between low weight at birth and many adult diseases in humans such as type 2 diabetes (1,2), cardiovascular disease (3), hypertension (4,5), and the metabolic syndrome (6,7). Body weight at birth is an indicator of the intrauterine environment, which could influence gene expression leading to phenotypes associated with disease. In this sense, the genetic makeup and gene profiling associated with such diseases could interact with body weight for gestational age at birth (8).

The peroxisome proliferator-activated receptor γ-2 gene is expressed in adipose tissue and regulates the differentiation and gene expression processes in adipocytes as well as glucose and lipid metabolism (9). Several variants in the PPARγ-2 gene have been identified, among them the Pro12Ala and the Ala12Ala genotypes in the PPARγ-2 isoform–specific exon B. Indeed, the Ala12 allele in exon B of this gene has been related to insulin sensitivity (10) and weight gain in young people (11) and adults (12).

The aim of the current study was to examine the effect of carrying the Ala12 allele of the PPARγ-2 gene in the relationship between body weight at birth and later body composition in adolescents.

METHODS

The adolescents included in this analysis belonged to the AVENA Study population (Alimentación y Valoración del Estado Nutricional en Adolescentes). The AVENA Study was designed to evaluate the nutritional status, dietary and leisure time habits, and physical activity and fitness of Spanish adolescents to identify risk factors for chronic diseases in adulthood. The complete methodology of this multicenter cross-sectional survey from five Spanish cities (13,14) (Santander, Granada, Murcia, Zaragoza, and Madrid) as well as the methodology used to calculate the subsample of adolescents with blood measurements have been described elsewhere (15). Briefly, the sampling was determined for the distribution of body mass index (BMI), which was the variable with the greatest variance for this age group (16). The minimum subject population was established at 1750 for the complete study and at 500 for a subgroup from whose members blood samples were required. Finally, the sample was adjusted by a weight factor to balance the sample in accordance to the distribution of the Spanish population and to ensure the representation of each group, already defined by age and sex. The final number of healthy white subjects included in the AVENA Study was 2859 adolescents, from which 581 (299 males and 282 females) had blood measurements.

For the analysis, we included those subjects whose data on birth weight, SES, gestational age, and anthropometric measurements were available. We also restricted the analysis to adolescents that were born at >35 wk of

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Abbreviations: FFM, fat-free mass; **FM,** fat mass; **PPARγ-2,** peroxisome proliferator–activated receptor γ-2

Table 1. *Raw birth weight data and birth weight for gestational age data according to the PPARγ-2 genotypes*

	Pro12Pro (n = 229)	Pro12Ala (n = 39)	Ala12Ala (n = 5)	p*
Birth weight (g)	3383.9 ± 543.7	3343.3 ± 422.7	3190.0 ± 655.2	0.969
Birth weight adjusted for gestational age and sex (g)	0.2 ± 539.7	−34.8 ± 408.4	−190.6 ± 663.1	0.993

* The p value from one-way analysis of variance.

gestation and with known physical activity and DNA data (273 adolescents, 133 males and 140 females).

Written informed consent was obtained from parents or guardians and subjects, and the complete study protocol was approved by the Ethical Committee of the Hospital Universitario Marqués de Valdecilla (Santander).

DNA samples. The polymorphisms of the PPARγ-2 gene were determined by the polymerase chain reaction method, and the genotypes were encoded as 1 = Pro12Pro, 2 = Pro12Ala, and 3 = Ala12Ala (17). The observed genotype frequencies of the polymorphism were in agreement with the Hardy-Weinberg equilibrium.

SES. According with the recommendations of the Spanish Society of Epidemiology, the SES was assessed by means of the educational level and the type of occupation of the father. According to this information, adolescents were classified into five categories: low, medium-low, medium, medium-high, and high SES (18).

Neonatal data. Birth weight and gestational age at birth were obtained from records kept in health booklets that are issued at birth and where child's pediatrician records birth weight, charts the infant's growth, vaccinations, etc. Birth weight was expressed as the SD from expected weight (Z score). It was calculated with the use of appropriate reference standards previously described for this population, according to sex and gestational age (19). Gestational age was coded as 1 (from 35 to 40 wk of gestation) or 2 (>40 wk of gestation).

Physical examination. Two trained anthropometrists carried out all the measurements in each city following the methods described below and elsewhere (20); one measured weight, height, and circumferences, and the other one measured skinfolds. Height (cm) was measured with a stadiometer to the nearest 0.1 cm (SECA, Vogel & Halke GmbH & CO. KG, Hamburg, Germany). Body weight was measured without shoes and with light clothing to the nearest 0.05 kg by using a beam balance (SECA, Vogel & Halke GmbH & CO. KG). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured with an nonelastic tape to the nearest 0.1 cm. Triceps and subscapular skinfold thickness were measured in triplicate with the use of a skinfold caliper (Holtain Ltd., Crymych, UK) on the left side (21), and the mean value was obtained (22–24). For all the skinfold thickness measurements, intraobserver technical errors of measurements were <1 mm and reliability was >95% (25). Skinfold thickness measurements were used to estimate fat mass (FM) (and hence percentage of body fat) by using the equations of Slaughter *et al.* (26,27). Fat free mass (FFM) was derived by subtracting FM from total body weight. Pubertal status was self-reported by the adolescents and classified according to the method of Tanner and Whitehouse (28). To study body fat distribution, two indicators of central adiposity were used: the subscapular-to-tricipital skinfold (STR) thickness ratio and waist circumference (29).

Overweight and obesity percentages were calculated using the criteria described by Cole *et al.* (30).

Physical activity. Physical activity index was calculated by means of four quantitative variables estimated by questionnaires, MET (metabolic equivalent) values of (1) activities pointed out on the summer period questionnaires, (2) daily physical activity for weekdays, and (3) Saturday, and (4) Sunday physical activities considering the academic year period (31).

Statistical analysis. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software 13.0 (SPSS Inc., Chicago, IL).

Mean values of unadjusted and adjusted birth weight according to the PPARγ-2 genotype was analyzed by one-way analysis of variance. Multiple regression analysis was performed to assess the associations between FFM or FM and the Z score for birth weight. The same model was done after controlling for age, Tanner stage, gestational age, SES, sex, and physical activity level. The Tanner stage categorical variable was transformed in four dummy variables to perform the regression analysis. The association between birth weight Z score and body composition was also adjusted for variation in body size by adjusting for BMI or height (32). We also tested the PPARγ-2 polymorphism × Z score birth weight interaction.

Results were expressed as mean ± SD unless indicated otherwise. A p value of ≤0.05 was defined as statistically significant.

RESULTS

A total of 229 (83.9%) of the adolescents carried the Pro12Pro genotype (Pro12Pro group), 39 (14.3%) carried the Pro12Ala genotype, and five (1.8%) carried the Ala12Ala genotype. Unadjusted and adjusted birth weight after controlling for gestational age and sex according to the PPARγ-2 genotype are shown in Table 1. There is no statistically significant association between the genotype and body weight at birth. Because the number of adolescents with the Ala12/Ala genotype was small, this subgroup was analyzed together with Pro12/Ala subjects. The frequency of the Ala12 allele was 0.161 in the studied population (Ala12 group).

The descriptive data, anthropometric variables, and body composition measurements of the 273 study subjects are shown in Table 2. The distribution of adolescents in the five SES levels considered in the two groups (Pro12Pro *versus* Ala12) was as follows: 4.8% *versus* 4.5% low, 23.6% *versus* 34.1% low-medium, 43.7% *versus* 29.5% medium, 21.4% *versus* 25.0% medium-high, and 6.6% *versus* 6.8% high SES level. Neither the SES (p = 0.729) nor physical activity index (p = 0.736) differed between PPARγ-2 groups.

In the Pro12Pro group, overweight and obesity percentages were 18.3% and 6.6%, respectively, and in the Ala12 group, overweight percentage was 15.9% and obesity percentage was 4.5%, and there were no statistically significant differences (p = 0.485). There was a significant interaction between birth weight Z score and PPARγ-2 gene polymorphisms in regard to later FFM (p = 0.045).

Table 2. *Characteristics of the subjects distributed according to PPARγ-2 gene polymorphism**

	Pro12Pro (n = 229)	Ala12 (n = 44)	p†
Age (y)	15.1 ± 1.32	15.0 ± 1.24	0.619
Tanner puberty stage			
I–II	8 (3.5%)‡	1 (2.3%)‡	
III–IV	136 (59.4%)‡	25 (56.9%)‡	
V	85 (37.1%)‡	18 (40.9%)‡	
Physical activity index	0.61 ± 0.448	0.50 ± 0.506	0.736
Birth weight (kg)	3.38 ± 0.543	3.33 ± 0.448	0.450
Z score	0.005 ± 0.5481	−0.0341 ± 0.4606	0.620
Weight (kg)	60.4 ± 13.11	60.6 ± 11.58	0.925
Height (cm)	165.7 ± 8.24	165.3 ± 9.29	0.800
BMI (kg/m^2)	21.9 ± 3.86	22.1 ± 3.43	0.754
Waist circumference (cm)	74.2 ± 9.43	75.1 ± 8.66	0.819
Subscapular SFT (mm)	13.1 ± 6.50	12.9 ± 6.37	0.815
Tricipital SFT (mm)	14.6 ± 6.28	14.9 ± 6.42	0.776
Ratio STR	0.92 ± 0.247	0.89 ± 0.242	0.385
Body composition§			
FFM (kg)	45.7 ± 0.5	46.4 ± 1.2	0.624
Fat mass (kg)	14.7 ± 9.10	14.2 ± 8.26	0.733
Body FM (%)	23.1 ± 9.08	22.8 ± 9.18	0.826

SFT, skinfold thickness.

* All values are arithmetic x ± SD, unless indicated otherwise.

† For the differences between the Pro12Pro and the Pro12Ala/Ala12Ala genotypes.

‡ Values are number and sample percentage.

§ Calculated from skinfold thickness measurements.

Table 3. *Unstandardized regression coefficients (β*) and SEs of the regression model examining association of Z score unadjusted with body composition variables in the two PPARγ-2 genotypes in adolescents*

	Unadjusted birth weight *Z* score			
	β	95% CI	SE	*p*
Pro12Pro (*n* = 229)				
Weight (kg)	4.653	1.583–7.724	1.558	0.003
Height (cm)	2.832	0.899–4.765	0.981	0.004
BMI (kg/m^2)	0.829	−0.087–1.744	0.465	0.076
FFM (kg)	2.154	0.347–3.962	0.917	0.020
FM (kg)	2.499	0.353–4.645	1.089	0.023
% FM	1.645	−0.510–3.800	1.094	0.134
Waist circumference	2.446	0.219–4.673	1.130	0.032
Ratio STR	−0.011	−0.090–0.067	0.040	0.776
Pro12Ala/Ala12Ala (*n* = 44)				
Weight (kg)	4.981	−2.692–12.654	3.802	0.192
Height (cm)	7.616	1.797–13.434	2.883	0.012
BMI (kg/m^2)	−0.114	−2.433–2.206	1.149	0.922
FFM (kg)	7.264	2.184–12.344	0.407	0.006
FM (kg)	−2.283	−2.820–3.253	0.127	0.410
% FM	−4.379	−10.435–1.678	0.220	0.152
Waist circumference (cm)	0.209	−5.646–6.064	2.901	0.943
Ratio STR	−0.019	−0.261–0.223	0.120	0.875

* Regression coefficients (*β*) represent change in body weight, height, BMI, and body composition measures per *Z* score increase in birth weight from expected.

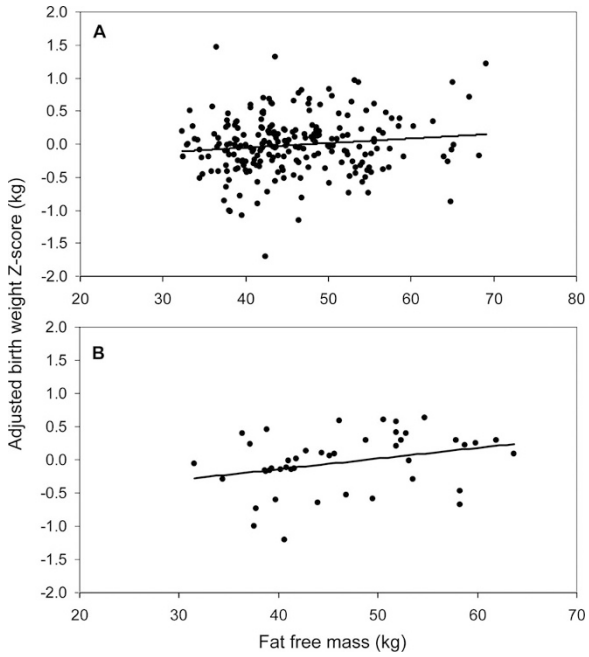

Figure 1. Bivariate correlations between adjusted birth weight *Z* score and FFM in the Pro12Pro genotyped adolescents ($r = 0.089$; $p = 0.182$) (*A*) and the Ala12 group ($r = 0.355$; $p = 0.018$) (*B*).

The relationships between birth weight with anthropometric and body composition measures in the two PPARγ-2 gene variant–related groups are shown in Tables 3 and 4 (unadjusted and adjusted models, respectively). In the Pro12Pro genotyped adolescents, unadjusted birth weight *Z* score was positively associated with current body weight ($p < 0.001$), height ($p < 0.001$), and FM ($p < 0.05$) (Table 3). Nevertheless, only the relationships with weight ($p < 0.01$) and FM ($p < 0.05$) remained significant after adjustment for age, Tanner stage, SES, physical activity, and sex, and they were diminished and became nonsignificant after adjustment with current BMI (Table 4) or height ($\beta = 0.110$; $p = 0.100$).

The relationship between birth weight *Z* score and FFM strongly differed between the two PPARγ-2 polymorphism–related groups. FFM was significantly associated with birth weight *Z* score in the unadjusted model in both Pro12Pro and Ala12 groups ($p < 0.05$ and $p < 0.01$, respectively) (Table 3), but this association remained significant after controlling for any of the potential confounding factors only in the Ala12

Table 4. *Regression analyses of body composition with birth weight Z score adjusted by different potential confounding variables*

	Z score adjusted for age, Tanner stage, SES, gestational age, physical activity, and gender				*Z* score adjusted for age, Tanner stage, SES, gestationalage, physical activity, gender, and BMI			
	*β**	95% CI	SE	*p*	*β**	95% CI	SE	*p*
Pro12Pro (*n* = 229)								
Weight (kg)	3.499	0.327–6.672	1.610	0.003				
Height (cm)	1.814	−0.186–3.814	1.015	0.075				
BMI (kg/m^2)	0.698	−0.242–1.638	0.477	0.145				
FFM (kg)	1.100	−0.764–2.963	0.507	0.246	0.635	−1.234–2.504	0.948	0.504
FM (kg)	2.400	0.198–4.601	1.117	0.033	1.084	−1.149–3.317	1.133	0.340
% FM	2.043	−0.155–4.241	1.115	0.068	0.576	−1.627–2.780	1.118	0.607
Waist circumference (cm)	1.268	−1.005–3.542	1.154	0.273	−0.362	−2.651–1.928	1.162	0.756
Ratio STR	0.014	−0.066–0.093	0.040	0.733	0.023	−0.057–0.102	0.040	0.574
Pro12Ala/Ala12Ala (*n* = 44)								
Weight (kg)	4.568	−3.643–12.782	4.070	0.268				
Height (cm)	6.222	−0.182–12.627	3.174	0.057				
BMI (kg/m^2)	0.099	−2.371–2.568	1.224	0.936				
FFM (kg)	6.164	0.562–11.766	2.776	0.032	5.762	0.146–11.378	2.783	0.045
FM (kg)	−1.596	−7.519–4.327	2.935	0.590	−3.265	−9.095–2.565	2.889	0.265
% FM	−2.682	−9.240–3.876	3.250	0.414	−2.682	−9.240–3.876	0.126	0.414
Waist circumference (cm)	0.132	−6.089–6.354	3.083	0.966	−1.796	−7.961–4.381	3.058	0.561
Ratio STR	0.040	−0.217–0.296	0.127	0.756	0.060	−0.195–0.315	0.126	0.635

* Unstandardized regression coefficients *β* represent change in body composition measure per *Z* score increase in birth weight.

group because it was largely unchanged in all considered regression models (Table 4). Among Pro12Pro carriers, this relationship was diminished after adjustment and became nonsignificant in the two regression models (Table 4) (Fig. 1).

When the influence of PPARγ-2 polymorphism on the relationship between birth weight *Z* score and body fat distribution was tested, the results showed that birth weight *Z* score was not associated with the STR in none of the two PPARγ-2 gene variant–related groups (Table 3) and that this association was unaffected by adjustment for potential confounders (Table 4). In the Pro12Pro group, waist circumference was significantly and positively associated with unadjusted *Z* score. However, this relationship became nonsignificant after adjustment in the two regression models (Table 4).

DISCUSSION

In the present study, we report that the Ala12 allele of the PPARγ-2 gene interacts in the relationship between low body weight for gestational age at birth and lower FFM in adolescents.

Before adjustment, birth weight *Z* score was significantly and positively related with later height and FFM in both groups, *i.e.* adolescents with the Pro12Pro or the Pro12Ala/Ala12Ala genotype. Conversely, unadjusted birth weight *Z* score was significantly associated with current weight and FM among adolescents with the Pro12Pro genotype. However, the relationship between birth weight and FM in adolescents with the Pro12Pro genotype became nonsignificant after controlling for possible confounding factors including current BMI.

The relationship between body weight at birth and lean body mass differed between the two PPARγ-2 gene variant–related groups. Thus, the association was positive and significant only among adolescents with the Ala12 allele on the PPARγ-2 after controlling for confounders.

Several recent studies found associations between low birth weight and increased metabolic risk of cardiovascular disease by programming small proportion of lean mass later in life (33,34). As reported in previously published articles, the programming of less lean mass by suboptimal fetal growth has been observed in which body composition measurements were obtained by dual energy x-ray absorptiometry (DXA) (32,35), by anthropometric methods (36), or by bioelectrical impedance (33). Conversely, the results showed that there were no PPARγ-2 gene polymorphism–related differences in the relationship between *Z* score birth weight and later body fat distribution.

It has been shown that gene and environment interact during development and weight at birth is an indicator of the early environment and growth. It has been previously proposed that PPARγ-2 gene could be a mediator of gene-environment interactions (37–39). The effect of Ala12 allele on BMI and type 2 diabetes has also been shown to be modified by dietary intake, degree of obesity, and physical activity level (Uusitupa *et al.*, Finnish Diabetes Prevention Study, 2001) (40).

To the best of our knowledge, the effect of PPARγ-2 gene polymorphisms in the relationship between body weight at birth and later body composition has not been previously reported. However, previous studies have observed strong interactions between the PPARγ-2 gene polymorphisms and birth weight on important metabolic factors such as insulin levels (41), homeostasis model assessment–insulin resistance index, and lipid metabolism (42). In this sense, Eriksson *et al.* reported that the Ala12 allele of the PPARγ-2 gene was associated with higher total cholesterol, low-density lipoprotein, and non–high-density lipoprotein cholesterol concentrations only among subjects whose birth weight was <3000 g (42).

We did not find differences in birth weight regarding the PPARγ-2 genotype categorization. This is good agreement with Pfab *et al.* (43) who reported that neither fetal nor maternal PPARγ-2 genotypes affected birth weight of the 1950 newborns studied.

The limitations of this study include the reduced sample size, as well as the different size of samples between the two groups, and the lack of more accurate measures of body composition, such as DXA. In this study, skinfold thickness measurements were used to estimate FM (and hence FFM) by using the equations of Slaughter *et al.*. Previously, we compared the most commonly used equations to predict body fatness from skinfold thickness in this particular population of male and female adolescents DXA as a reference method of fatness measurement. We had concluded that the accuracy of most of the skinfold thickness equations for assessment of body fat percentage was poor at the individual level. However, to predict body fat percentage when a relative index of fatness is required in field or clinical studies, Slaughter *et al.* equations may be used in adolescents of both sexes (26).

In summary, this study shows that after controlling for age, Tanner stage, SES, gestational age, physical activity, sex, and BMI or height, FFM decreases with decreasing birth body weight in adolescents carrying the Ala12 allele of the PPARγ-2 gene. This finding confirms the role of carrying this specific genotype in the relationship between birth weight and body composition in adolescents.

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