

# Etiologic and Cardiovascular Risk Factors in Obese Children From Extremadura in Spain. Their Relationship With Insulin Resistance and Plasma Adipocytokine Levels

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**Introduction and objectives.** The aim was to investigate etiologic and cardiovascular risk factors in obese children from Extremadura, Spain, and their relationship with insulin resistance and plasma adipocytokine levels.

**Methods.** The study included 373 children (age, 3-13 years) who were randomly selected from schools in the city and province of Badajoz and from 2 health centers in the Spanish autonomous community of Extremadura.

**Results.** Some 9.5% of children were obese. Compared with normal weight children, obese children exhibited a greater weight gain in the first year of life (7.3 [1.5] kg vs 6.3 [0.8] kg), were less physically active (9.6 [7.2] h/week vs 13.1 [8.1] h/week), and had more screen time (18.0 [12.4] h/week vs 12.8 [8.2] h/week), a lower high-density lipoprotein cholesterol level (46.0 [11.4] mg/dL vs 64.6 [22.9] mg/dL), higher arterial systolic pressure (102.3 [8.5] mm Hg vs 89.9 [13.4] mm Hg), increased insulin resistance (6.2 [3.6] vs 4.6 [4.5]), a higher level of leptinemia (24.8 [13.8] ng/mL vs 12.9 [10.8] ng/mL), and a lower level of adiponectinemia (8.4 [5.7] µg/mL vs 15.6 [7.9] µg/mL).

**Conclusions.** Our findings demonstrate that there is a relationship between a sedentary lifestyle and the development of insulin resistance and altered adipocytokines levels in obese children, and that these changes are related to a number of cardiovascular risk factors.

**Key words:** Children. Obesity. Cardiovascular risk. Insulin resistance. Adipocytokines. Extremadura.

## Factores etiológicos y de riesgo cardiovascular en niños extremeños con obesidad. Su relación con la resistencia a la insulina y la concentración plasmática de adipocitocinas

**Introducción y objetivos.** Se estudian factores etiológicos y de riesgo cardiovascular en niños extremeños obesos y su relación con la resistencia a la insulina y la concentración plasmática de adipocitocinas.

**Métodos.** Se estudió a 373 niños (de 3 a 13 años de edad) seleccionados aleatoriamente en colegios de Badajoz capital y provincia y en dos centros de salud de la Comunidad de Extremadura.

**Resultados.** Un 9,5% de los niños eran obesos. Respecto a los normopesos, en los obesos el incremento de peso al primer año de vida estaba aumentado (7,3 ± 1,5 frente a 6,3 ± 0,8 kg), la actividad física total estaba disminuida (9,6 ± 7,2 frente a 13,1 ± 8,1 h/semana), el tiempo de pantalla estaba aumentado (18 ± 12,4 frente a 12,8 ± 8,2 h/semana), el colesterol de las lipoproteínas de alta densidad estaba disminuido (46 ± 11,4 frente a 64,6 ± 22,9 mg/dl), la presión arterial sistólica estaba aumentada (102,3 ± 8,5 frente a 89,9 ± 13,4 mmHg), la resistencia a la insulina estaba aumentada (6,2 ± 3,6 frente a 4,6 ± 4,5), la leptinemia estaba aumentada (24,8 ± 13,8 frente a 12,9 ± 10,8 ng/ml) y la adiponectinemia estaba disminuida (8,4 ± 5,7 frente a 15,6 ± 7,9 µg/ml).

**Conclusiones.** Se muestra la relación entre sedentarismo y desarrollo de insulinorresistencia y alteraciones de la concentración de adipocitocinas en la obesidad infantil y su relación con algunos factores de riesgo cardiovascular.

**Palabras clave:** Niños. Obesidad. Riesgo cardiovascular. Resistencia a la insulina. Adipocitocinas. Extremadura.

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## INTRODUCTION

Child obesity is the main concern of pediatric healthcare in the developed world.<sup>1,2</sup> It is frequently associated with cardiovascular risk factors such as elevated blood pressure, dyslipidemia, hyperinsulinemia, or increase in left

## ABBREVIATIONS

BMI: body mass index  
 HDL: high-density lipoprotein  
 HOMA: homeostasis model assessment index

ventricular mass.<sup>3-5</sup> In Spain, the situation is similar to that in other developed countries.<sup>6-9</sup>

Despite universal recognition of the problem, agreement is not unanimous regarding the causes of child obesity<sup>10</sup> or the etiopathogenic mechanisms involved.<sup>1,2,11</sup> Child obesity depends to a great extent on nutrition, physical activity and the child's family, and culture.<sup>2</sup>

A high percentage of obese children and adolescents (more than 80% in some studies) also present other components of cardiometabolic syndrome, such as insulin resistance, altered adipocytokine secretion, hypertriglyceridemia, low concentrations of high-density lipoprotein cholesterol (HDL-C), or elevated blood pressure.<sup>3,12-16</sup> According to several studies, 18%-30% can be diagnosed with cardiometabolic syndrome depending on the criteria used.<sup>8,15</sup>

The basic aim of the present study was to obtain more information on child obesity in Spain. Thus, children from rural and urban areas in the autonomous community of Extremadura, Spain, were studied to investigate the association of obesity with the following: *a*) etiologic factors, such as weight gain in the first years of life, overeating, and a sedentary lifestyle; *b*) plasma lipid levels, blood pressure, and heart rate; and *c*) the association between childhood obesity and peripheral insulin sensitivity or insulin secretion and plasma leptin, adiponectin and resistin concentrations.

## METHODS

The first part of the study consisted in analyzing a sample of children aged 3-12 years from the autonomous community of Extremadura, Spain, randomly selected from schools in the city of Badajoz, Spain, and from 2 towns (Olivenza and Los Santos de Maimona) randomly selected from other cities in the province. Data collection was conducted at the beginning of mid-morning break, before any type of food was taken. Anthropometric measurements were performed by accredited personnel trained for this, with the child in underwear, using a portable digital stadiometer and a weighing apparatus correctly calibrated for this purpose. Overweight or obesity was diagnosed when the body mass index (BMI)—the weight in kilograms divided by the square of the height in meters—exceeded the cutoff points for age and sex, according to the criteria proposed by Cole

et al.<sup>17</sup> Glucose concentrations and total cholesterol were determined in blood obtained from the finger using reactive strips (Accutrend, Roche Diagnostics, Mannheim, Germany) which have an accuracy of >90% for both tests. The parents or tutors of the participants completed a questionnaire that included a quantitative continuous diet record for 7 days,<sup>18</sup> quantification of physical activity during this period (hours playing outside the house and sports activities), and an index relating to sedentary lifestyle (number of hours the child spent in front of a screen: television, computer, and video-console). Eating habits were quantified using the validated<sup>19</sup> Alimentación y Salud (Eating and Health) software program, versión 0689.01 (BitASDE General Médica Farmacéutica, Valencia, Spain) from the Instituto de Nutrición y Tecnología de los alimentos, University of Granada, Spain.

The hormonal study was performed in 86 randomly selected children attending 2 pediatric services (Centro de Salud San Jorge, Cáceres, Extremadura, Spain and Centro de Salud La Paz, Badajoz, Extremadura, Spain) for everyday medical problems unrelated to cardiovascular or metabolic alterations. All the participants completed a 7-day questionnaire with the same characteristics as the one used in first part of the study, to which was added data on weight at birth and during the first year of life based on pediatric medical records.

As described, anthropometric measurements were taken in the morning, after the children had fasted since the previous night. Overweight was diagnosed via the BMI using the same criteria described above. Blood pressure and heart rate were consecutively measured 3 times by pediatric nursing personnel using a mercury sphygmomanometer with cuffs adapted for age and size. A venous blood sample was taken which was used to determine the following: blood glucose (glucose HK assay, automatic analyzer), triglyceridemia (Chod-pad assay, automatic analyzer), plasma total cholesterol concentration (Chod-Pad assay, automatic analyzer), and HDL-C (HDL-C plus assay, automatic analyzer), insulinemia (Human insulin RIA kit, Linco research, Missouri, USA), plasma leptin concentration (Human leptin RIA assay kit, Linco), adiponectin (Human adiponectin RIA assay kit, Linco), and resistin (Human resistin ELISA kit, Linco). Insulin resistance was indirectly estimated using the HOMA (homeostasis model assessment index: blood glucose [in mmol/L] × insulinemia [in µU/mL]/22.5).<sup>20</sup>

The study followed the ethical guidelines recognized by the Declaration of Helsinki (revised Hong-Kong, September 1989 and Edinburgh, 2000) and was conducted according to the EEC Good Clinical Practice recommendations (document 111/3976/88, July 1990) and current Spanish legal regulations which govern clinical research on humans (Royal Decree 561/1993 on clinical trials) and was approved by the of Bioethics Committee of the University of Extremadura, Spain.

**TABLE 1. Characteristics of the Children Randomly Selected From the Schools Studied, Anthropometric and Nutritional Parameters, Physical Activity, and Metabolic Measurements**

	Normal Weight	Overweight	Obese
Subjects, n	158	88	43
Age, mean (SD), y	9.3 (2.1)	9.7 (1.7)	9.3 (2.3)
Age, range, y	3-12	3-12	4-11
Boys/girls, n	88/70	48/40	24/19
BMI	16.9 (1.9)	21.7 (2) <sup>a</sup>	25.8 (3.8) <sup>a</sup>
kcal/wk	15 467 (2321)	14 371 (2181) <sup>b</sup>	13 558 (2527) <sup>b</sup>
Proteins, %	16.1 (2)	16.7 (2.5)	17.2 (2.5)
Glycosides, %	45.6 (4.2)	45 (4.5)	45.8 (4.5)
Fats, %	37.9 (3.9)	37.9 (3.8)	36.7 (3.9)
Physical activity, h/wk	13.1 (8.1)	11.8 (7.8)	9.6 (7.2) <sup>b</sup>
Onscreen time, h/wk	12.8 (8.2)	14.6 (8.9)	18 (12.4) <sup>a</sup>
Glycemia, mg/dL	86.2 (15.8)	87.1 (17.2)	87.6 (18.1)
Cholesterolemia, mg/dL	155.3 (16.6)	155.7 (14.1)	157.1 (18.4)

Data are expressed as mean (standard deviation) except where otherwise indicated.

<sup>a</sup> $P < .01$ .

<sup>b</sup> $P < .05$ .

Statistical analysis of the results included a comparison of means using the Student *t* test for independent samples, the Levenne test for equality of variances and a correlation analysis of the variables using Pearson's correlation. The data was tested for normality using the Kolmogorov-Smirnov test. Analysis of the association between the different factors and obesity was performed by stepwise logistic regression, with obesity as the dependent variable, and the odds ratio (OR) was calculated for each independent variable. Statistical analyses were performed using the SPSS statistical software package, version 13, for Windows. All values were expressed as mean (standard deviation) and a *P* value less than .05 was considered statistically significant.

## RESULTS

As shown in Table 1, and based on the questionnaires completed by the parents or tutors, the total energy intake showed that the overweight children consumed fewer kilocalories during the week than children with normal weight. No statistically significant differences were found in the percentages of macronutrients ingested in any of the 3 groups. Total physical activity was significantly less in the obese children. Onscreen time was significantly higher in the obese children compared to the other 2 groups. There were no significant differences in blood glucose and total cholesterol concentrations between the 3 groups.

As shown in Table 2, the increase in BMI was accompanied by a parallel increase in waist circumference and the correlation between the parameters was  $r = 0.841$  ( $P < .001$ ) in all subjects ( $n = 84$ ). No significant differences were found between birthweight in normal weight children, overweight children, and obese children (3.3 [0.4] kg, 3 [0.5] kg, and 3.1 [0.54] kg, respectively), but

weight-gain during the first year of life was significantly greater in overweight and obese children than in the normal weight children. No significant differences were found between the 3 groups in the total number of kilocalories ingested during the week studied. Neither were significant differences found in the percentages of macronutrients ingested by the 3 groups. Total physical activity was significantly less ( $P < .05$ ) in the obese children than in the other 2 groups. The sedentary lifestyle index, expressed in total onscreen hours (the sum of hours spent on television, computer, and video games) was significantly higher in obese children.

The only change in lipid concentrations (Table 3) that could be detected was a significant decrease in HDL-C levels in the overweight and obese children compared to normal weight children. Differences in triglyceride concentrations between the 3 groups did not reach statistical significance. Regarding cardiovascular parameters (Table 3), systolic blood pressure was significantly higher in overweight and obese children than in normal weight children. Diastolic blood pressure was significantly higher ( $P < .05$ ) in the obese children.

The data shown in Table 4 indicate insulin resistance in the obese children. Blood glucose concentrations were normal and similar in the 3 groups. Insulinemia was significantly higher among the obese children and, thus, the HOMA index was also significantly higher among them. Leptin concentrations were significantly higher ( $P < .05$ ) in obese children, whereas their adiponectin concentrations were lower ( $P < .05$ ). No significant differences were found between groups in plasma resistin concentrations.

As shown in Table 5, the logistic regression analysis indicated significant associations between the dependent variable obesity and the following independent variables: sedentary lifestyle as an etiological factor, defined as low

**TABLE 2. Characteristics of the Children Randomly Selected From the Health Centers, Anthropometric and Nutritional Parameters, and Measured Physical Activity**

	Normal Weight	Overweight	Obese
Subjects, n	20	36	28
Age, mean (SD), y	10.8 (2.7)	10.4 (1.6)	10.3 (2.3)
Age, range, y	6-13	6-13	5-13
Boys/girls	9/11	20/16	15/13
BMI	18.6 (2.1)	23 (1.7) <sup>a</sup>	27.5 (3.4) <sup>a</sup>
Waist circumference, cm	65.7 (9.2)	78.6 (8.3) <sup>b</sup>	85.7 (3.4) <sup>a</sup>
Weight gain per year, kg	6.3 (0.8)	7.1 (1.2) <sup>b</sup>	7.3 (1.5) <sup>b</sup>
Energy intake, kcal/wk	14 870 (2412)	14 089 (2628)	13 684 (2841)
Physical activity, h/wk	10.2 (7.6)	11.4 (8)	6.4 (7.2) <sup>b</sup>
Onscreen time, h/wk	15.5 (7.1)	16.9 (9)	20.1 (13.6) <sup>b</sup>

BMI: body mass index.

<sup>a</sup>*P*<.01.<sup>b</sup>*P*<.05.**TABLE 3. Cardiovascular and Lipid Parameters in the Children Selected From Health Centers**

	Normal Weight	Overweight	Obese
Subjects, n	20	36	28
Total cholesterol, mg/dL	179.2 (29.9)	170.8 (42.3)	170 (21.9)
HDL-C, mg/dL	64.6 (22.9)	50.3 (13.4) <sup>a</sup>	46 (11.4) <sup>a</sup>
Triglycerides, mg/dL	60.8 (27.2)	64.9 (36.4)	70.5 (32.3)
Heart rate, beat/min	74.5 (9.1)	78.4 (8)	76 (9.4)
SBP, mm Hg	89.9 (13.4)	97.5 (10.9) <sup>a</sup>	102.3 (8.5) <sup>a</sup>
DBP, mm Hg	46.7 (8.5)	51.1 (13.8)	50.7 (6.7) <sup>a</sup>

DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure.

<sup>a</sup>*P*<.05.**TABLE 4. Evaluation of Insulin Resistance and Plasma Adipocytokine Concentrations Measured in the Children Selected From Health Centers**

	Normal Weight	Overweight	Obese
Subjects, n	19	33	26
Glycemia, mg/dL	81.7 (5.1)	81.6 (7.4)	82.6 (5.7)
Insulin, $\mu$ U/mL	22.8 (23.1)	21.3 (11.8)	30.4 (17.5) <sup>a</sup>
HOMA	4.6 (4.5)	4.2 (2.6)	6.2 (3.6) <sup>b</sup>
Leptin, ng/mL	12.9 (10.8)	17.7 (11.8)	24.8 (13.8) <sup>a</sup>
Adiponectin, $\mu$ g/mL	15.6 (7.9)	9.6 (6.5) <sup>a</sup>	8.4 (5.7) <sup>a</sup>
Resistin, ng/mL	21.6 (8.1)	22.2 (19.4)	23.5 (13.3)

HOMA: homeostasis model assessment index (described in the text).

<sup>a</sup>*P*<.05.

physical activity and a high number of onscreen hours; cardiovascular risk factors associated with obesity, such as high systolic blood pressure and low HDL-C concentrations, and the association with higher levels of leptinemia.

## DISCUSSION

The obesity rate found in the present study (9.5%) coincides with that found in recent studies conducted in other Spanish autonomous communities and provinces, such as the one conducted in Cuenca (8.8%),<sup>6</sup> the Four Provinces study (9.5%),<sup>9</sup> and the EnKid<sup>21</sup> study

(8.5%) when the criteria developed by Cole et al<sup>17</sup> were applied.

Child obesity seems to be result of a multifactorial process involving genetic and environmental factors.<sup>2</sup> Numerous studies have reported that rapid weight gain in the first months of life can have anthropometric, metabolic, and cardiovascular implications in the long-term.<sup>1,22</sup> Our results confirm that weight gain during the first year of life was significantly greater in overweight and obese children than in those of normal weight. No significant differences in birthweight were detected in relation to child obesity, which coincides with the findings of the Four Provinces study.<sup>23</sup>

**TABLE 5. Logistic Regression Analysis Showing the Independent Variables Significantly Associated With the Dependent Variable Obesity**

Variables	OR (95% CI)	Probability	P
Low physical activity (n=373)	2.558 (1.25-5.234)	0.01	<.05
Onscreen time (n=373)	2.369 (1.182-4.748)	0.015	<.05
SBP (n=84)	8.615 (2.316-32.045)	0.001	<.01
HDL (n=84)	4.136 (1.482-11.546)	0.007	<.01
Leptin (n=84)	3.281 (1.224-8.79)	0.018	<.05

CI: confidence interval; HDL: high-density lipoproteins; OR: odds ratio; SBP: systolic blood pressure.

It seems reasonable to assume, at least from a theoretical standpoint, that excessive total calorie intake and the consumption of food high in calories should play a relevant role in the development of child obesity.<sup>10,24</sup> However, and paradoxically, this association is not well-defined, partly due to there being few studies on child obesity which have analyzed total calorie intake in detail.<sup>2-4</sup> Thus, a recent review addressing this subject<sup>2</sup> highlighted the discrepancy confirmed in the United States, where the increase in obesity among adolescents was associated with a reduction in energy intake. Our study does not show a significant increase in energy intake among overweight children compared to those of normal weight in any of the 2 groups studied. In other studies on Spanish children, overweight was only associated with a diet “moderately high in calories.”<sup>12,23</sup> Many factors could account for these discrepancies, among which is the methodology used to calculate daily energy intake. Given the characteristics of the sample, it was not possible to analyze differences in children grouped by age and sex.

On the other hand, the association between a high-calorie diet and obesity could be due to a lack of balance between energy intake from food and energy expenditure due to physical exercise.<sup>25</sup> Without doubt, a sedentary lifestyle is the etiological factor most frequently assessed in all studies on child obesity, regardless of where they were performed.<sup>1,2</sup> Several studies conducted in Spain stress the relevance of a sedentary lifestyle to child and adolescent obesity and cardiovascular risk.<sup>26,27</sup> Our results show that weekly physical activity, that is, the total number of hours playing outside and sports activities, was significantly low in obese children. On the other hand, the sedentary lifestyle index, expressed in the number of hours a week the children spend onscreen (television, video games, and computer) was significantly higher in obese children. Our results agree with those of other studies conducted in Spain<sup>28</sup> and other countries<sup>29</sup> and show a significant association between obesity and low physical activity (OR=2.558;  $P<.05$ ) and sedentary lifestyle (onscreen time, OR=2.369;  $P<.05$ ).

Child obesity is frequently associated with cardiovascular and metabolic problems and in particular with insulin resistance and cardiometabolic syndrome.<sup>3,7,8,16,30,31</sup> Few studies have investigated fat

distribution among obese children and its association with cardiovascular risk factors,<sup>32</sup> although some have been conducted in Spain.<sup>33</sup> The changes in lipid concentrations found in the obese children, and especially the significant decreased HDL-C concentrations, agree with the published data, as well as with several studies conducted in Spain.<sup>12,13</sup> Our results also agree with other studies regarding the absence of significant changes in triglyceride concentrations.<sup>6</sup> In the present study, low HDL-C concentrations were significantly associated (OR=4.136;  $P<.01$ ) with child obesity. Increased blood pressure in the obese children is another of the effects of this alteration, which is universally recognised.<sup>34,35</sup> In our study, systolic and diastolic blood pressure were significantly higher in the obese children. These results are in line with those shown by other studies in Spain<sup>6</sup> and other countries.<sup>34,35</sup> In our study, only systolic blood pressure had a significant association with obesity (OR=8.615;  $P<.01$ ).

Child obesity is frequently accompanied by alterations in insulin secretion or sensitivity.<sup>3,7,8,11,16,30,31</sup> Insulin resistance is a cardiovascular risk factor and its presence among the young could be a risk marker of future coronary mortality.<sup>12</sup> The HOMA index was significantly higher among the obese children. Similar results have been found in studies conducted in other countries<sup>11</sup> and Spain.<sup>9,12</sup>

Adipose tissue, in addition to storing energy, also produces adipocytokine.<sup>36,37</sup> Leptin is a key hormone in appetite regulation and controlling the size of fatty deposits.<sup>15</sup> Some studies conducted in obese children have shown that leptin concentrations are higher than in normal weight children, thus indicating leptin resistance in those children.<sup>38</sup> Our data support this viewpoint, since plasma leptin concentrations were higher in the obese children and were significantly associated (OR=3.281;  $P<.05$ ) with child obesity. Several studies have confirmed that adiponectin concentrations negatively correlate with BMI, waist diameter, and insulin and triglyceride concentrations in obese children and adolescents, and positively correlate with HDL-C concentrations in obese subjects.<sup>39,40</sup> Our results support these published results, and confirm that decreased adiponectin concentrations can be a strong predictor of the insulin resistance and

obesity in children.<sup>15</sup> Resistin is another adipocytokine that has been implicated in insulin resistance, although data obtained from studies on humans are contradictory.<sup>41</sup> Our results, in agreement with those from other published studies, do not support an association between resistin and insulin resistance and obesity in children.<sup>41-43</sup>

## CONCLUSIONS

The child obesity rate was 9.5%, which is similar to that found in the rest of Spain. Two relevant etiological factors are weight-gain during the first year of life and sedentary lifestyle. Child obesity is associated with 2 basic cardiovascular risk factors: increased systolic blood pressure and decreased plasma HDL-C concentrations. Obese children present insulin resistance accompanied by increased leptin concentrations and decreased adiponectin concentrations.

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