Rapid infant weight gain is associated with excess adiposity at 7-years of age in children from Aragon, Spain

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**ABSTRACT**

**Background:** Infants with rapid weight gain (RWG) during the 1\textsuperscript{st} year are at increased risk of overweight.

**Objective:** To examine its associations with body mass index z-score (BAz), fat mass index (FMI) and free fat mass index (FFMI) in 7 y-old Spanish children from the CALINA study.

**Methods:** Dual X – Ray Absorptiometry scans and weight and height measurements were conducted. RWG was defined as a positive change in weight/age Z-score greater than 0.67 from birth to 6 months (0–6 m), 6 to 12 months (6–12m) and 0 to 12 months (0–12m). Adjusted linear regressions were performed.

**Results:** A RWG from 0-6m, 6-12m and 0-12m was associated with BAz in children (B = 0.607, B = 0.522 and B = 0.649, p ≤ 0.001 in all cases), specifically in boys with RWG from 0-6 m (B = 0.734, p = 0.001) and in girls from 6 to 12 m (B = 0.678, p = 0.006). RWG predicted FMI in children with RWG from 6-12 m (B = 0.590, p = 0.008), being significative only in girls (B = 1.259, p = 0.001) and in children with RWG from 0-12 m (B = 0.493, p = 0.024), being significative only in boys (B = 0.593, p = 0.035). FFMI was higher in those with RWG from 0-6 m, 6-12 m and 0-12 m (B = 0.618, B = 0.468, B = 0.575 p < 0.001 in all cases), being significative in boys in all periods (B = 0.657, B = 0.411, B = 0.579, p < 0.021 in all cases) and in girls that developed RWG from 0-12 m (B = 0.380, p = 0.049)

**Conclusions:** In a subsample from the CALINA Study, there are associations between RWG in the 1\textsuperscript{st}Y and BAz, FMI and FFMI at 7 years.

**ARTICLE HISTORY** Received 8 May 2020; Accepted 12 December 2020

**KEYWORDS** Childhood obesity; adiposity; growth and development; body mass index; fat mass index; free fat mass index

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AbbreviationsRWG: Rapid weight gain; CALINA Study: Crecimiento y Alimentación en La Infancia en Niños Aragoneses (in Spanish); DXA: Dual X-Ray Absorptiometry; BAz: Body Mass Index z-score; FMI: Fat Mass Index; FFMI: Free Fat Mass Index.

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Introduction

Childhood obesity is a multifactorial disease associated with a wide range of serious health and social consequences including a higher risk of premature death and disability in adulthood (WHO 2018). Its prevalence is still increasing worldwide (Reilly 2006) and children and adolescents are part of the affected population. Obesity is defined as an excess of body fat that is harmful to the general health status. This definition is expressed in terms of body fat content, but in clinical practice and epidemiology, body fat content can rarely be measured with acceptable precision and accuracy (Reilly 2006; Vicente-Rodriguez et al. 2012). According to the latest European surveillance, Mediterranean countries still have the highest prevalence’s of overweight and obesity among Europe and Spain is not an exception. With a 42% of the overweight in boys, from which 19% represent obesity and a 41% of the overweight in girls, from which a 17% represents obesity, Spain is the second country after Cyprus with the highest rates of overweight and obesity (Rito et al. 2019).

Childhood obesity is the consequence of complex interactions of genetic, environmental, social and behavioural factors. Foods, nutritional components, and food intake patterns may be associated with the increasing obesity prevalence in children (Huang and Qi 2015). Perinatal factors, such as low birth weight are also important, given that children with this condition are used to have rapid weight gain (RWG) during early postnatal life has been associated with increased long-term obesity risk factors like central obesity, insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertension, increased fat mass, and cardiovascular disease later in life (Hong and Chung 2018; Larque et al. 2019).

RWG, which is considered as a positive change in the weight for age Z-Score higher than 0.67 during a defined period during the first years of life (Monteiro and Victora 2005), is a condition that not only affects infants with low birth weight or prematurity, and it has several impacts on health outcomes. Studies assessing RWG and later weight and adiposity outcomes have found a positive relationship with overweight and obesity (Iguacel et al. 2018) regardless of birth weight (Stettler et al. 2002) and specific fat indicators like body fat mass (Chomtho et al. 2008; Nanri et al. 2017). In fact, a previous systematic review and metanalysis by Zheng et al. (Zheng et al. 2018) RWG in infancy was associated with overweight/obesity from childhood to adulthood that RWG during infancy is a significant predictor of adiposity in later life.

The association between RWG and later weight status is well known, nevertheless, given that a better approach for assessing body composition is the use of mass indexes like fat mass index (FMI) and free fat mass index (FFMI), the aim of this study was to assess RWG from 0 to
12 months considering perinatal factors and determine its influence in body mass index z score (BAz), fat mass index FMI and FFMI in 7-year-old children from Aragon Spain who were followed prospectively from birth.

Materials and methods

Study population: The CALINA study

We conducted a transversal secondary analysis using data from the study Growth and Feeding during Lactation and Early Childhood in Children of Aragon (Crecimiento y Alimentación en La Infancia en Niños Aragoneses, CALINA in Spanish), which is a cohort study whose sampling design is described in detail elsewhere (Oves Suarez et al. 2014). Briefly, CALINAs main objective was to study the pattern of growth and feeding of a representative sample of children born from March 2009 to February 2010 in the Autonomous Community of Aragon in Spain. Participants included (n = 1465) were examined at birth and periodically re-examined in primary care centres at 2 weeks of age, monthly (after 1, 2, 4, 5 and 9 months) and yearly (1, 2, 4 and 6 years later). After 7 years, a new cohort was evaluated as part of a second project with the CALINA sample. Given that this cohort could only be performed in the body composition laboratory of The University of Zaragoza, only children from the initial cohort with residence in Zaragoza (n = 1119, which represented a 72.0% of the baseline sample) were invited to participate. Because many of them had moved out of the city, refused to participate or had incomplete data, the CALINA cohort at 7 year included 420 children, from which, 356 children fulfilled the inclusion criteria for the present study and were therefore included in this study, representing 24.3% from the baseline sample. Participants from the other two regions of Aragon, Huesca and Teruel were not included in the 7year-old cohort.

Inclusion criteria

Inclusion criteria for the present study was to have bodyweight data at birth and 6 and/or 12 months of age and Dual X-Ray Absorptiometry (DXA) body composition assessment at 7 years of age (7y). Differences between socio-economic characteristics of the included and the excluded sample were analyzed, and significant differences were observed in maternal age (33.2 years in the included vs. 31.5 years in the excluded sample, p = 0.000), origin (10.4% of the immigrants in the included sample vs. 31.2% in the excluded sample, p = 0.000), and education (19.3% of the low-educated mothers in the included
sample vs. 32.0% in the excluded sample and 45.1% of the high-educated mothers in the included sample vs. 34.0% in the excluded sample, p = 0.000).

**Ethical approval**

The study was performed following the ethical guidelines of the Declaration of Helsinki 1964 (Group BMJP 1996). Parents or legal guardians provided signed consent and verbal assent was obtained from each child. Ethical approval for the initial cohort in June 2008 (P108/0021) and for the 7y-measurements in 2016 were obtained from Aragon’s Committee of Ethics in Clinical Research (Comité de Ética de la Investigación de la Comunidad de Aragón, CEICA). Parents or legal guardians provided signed consent for participation.

**Measurements and procedure**

**Independent variables: rapid weight gain**

In order to compare means of BAz, FMI and FFMI, we categorized the sample into groups according to the variable “RWG” during three different periods of time: 0–6 m, 6–12 m and 0–12 m. RWG is defined as a positive change in the weight for age z-score higher than 0.67 during a defined period during the first years of life (Monteiro and Victora 2005). Bodyweight was measured to the nearest 10 g using a weight scale/bioelectric impedance instrument (Tanita * BC-418, Corporation of America, Inc., IL, USA) and child length was measured using a recumbent board, both measurements were performed in each visit from the first by health-care professionals, including dietitians, nurses and medical doctors. Determination of z-score values of weight for age for girls and for boys was performed using the World Health Organization (WHO) Anthro Software * (v 3.2.2, Geneva, Switzerland), according to the WHO growth standards of 2006–2007 (WHO 2006).

**Outcome variable: adiposity indicators**

**BMI z-score (BAz)**

Weight and standing height at the 7y evaluation was measured by the researchers of the present study and data were collected from September 2016 until June 2017. Children’s height was measured to the nearest 0.1 cm with his or her shoes removed using a stadiometer (SECA 225, SECA, Hamburg, Germany) and body weight was measured to the nearest 0.1 kg using a weight scale/bioelectric impedance instrument (Tanita * BC-418, Corporation of America, Inc). BMI was calculated and converted to Z-Scores (BAz) by calculating it with the Anthro Plus Software * (v 1.0.4, Geneva, Switzerland), according to the WHO Growth reference (WHO 2000).
BAz were chosen as the main weight indicator because its scale is the linear scale and therefore permits the analyses of statistics such as means, standard deviations and standard errors. Moreover, the z scores are helpful for grouping data by age and sex (Mei and Grummer-Strawn 2007).

**Fat mass index (FMI) and free fat mass index (FFMI)**
Whole-body dual-energy X-ray absorptiometry (DXA) scans were performed with the pediatric version of the QDR Explorer software (Hologic Corp. Software version 12.4. Bedford, MA, USA). DXA equipment was calibrated before each assessment with a lumbar spine phantom and step densities phantom following the Hologic guidelines. Scans were conducted by trained researchers. The analysis was performed without considering the head composition. Values for the total body and bone regions included total mass (grams), Bone Mineral Content (grams), bone area (cm²), areal bone mineral density (gm/cm²), fat mass (gm), lean mass excluding BMC (gm), lean mass including BMD (gm) and per cent body fat. The outcome variables were obtained by the DXA assessment were FMI, a continuous variable calculated for each participant as subtotal fat mass in kilograms/height in meters² and FFMI, which was calculated as subtotal lean fat mass in kilograms/height in meters².

**Potential confounding factors**

**Demographic information**
Data regarding ethnic and the country origin and maternal level of education were collected at study entry. For this study, parental education was classified into three categories: elementary, elementary to secondary and bachelor or higher. Maternal age was recorded as the age at child’s birth and children’s age was calculated at the day of the visit.

Perinatal factors were gathered from the clinical history of participants. These factors included gestational age (GA), which was categorized into <37 weeks (preterm) and 37–42 weeks (term), birthweight classification low birth weight (<2,500 g) (UNICEF and WHO 2004), appropriate birth weight (2,500 – <4000 g) and macrosomic (>4000 g) (Henriksen 2008) and maternal perinatal factors like BMI before pregnancy and weight gain during pregnancy depending on the BMI before pregnancy were observed and defined as insufficient, adequate or excessive according to The Institute of Medicine and The National Research Council from the United States (Rasmussen and Yaktine 2009). Smoking during pregnancy was also assessed.
**Statistical analysis**

Participants were described in terms of demographic and anthropometric characteristics. Characteristics of subjects at infancy and childhood were stratified by sex and presented as frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Regarding outcome variables, first, assessment of normality of continuous variables was performed graphically and numerically. Differences in outcome variables based on possible influential covariates were assessed (data not have shown). For this step, continuous variables were analyzed with T-tests (BAz) when normally distributed or with the Mann–Whitney U test for non-normally distributed variables (FMI and FFMI). Categorical data were analyzed with T-Test and Analyses of Variance (ANOVA) when normally distributed and Mann–Whitney or Kruskal Wallis for abnormally distributed data. The ANalyses of COVariance (ANCOVA) was used to compare the adjusted means of the BAz, FMI and FFMI between those who present RWG in the periods of time explained above adjusting for influential covariates perinatal variables of the mother (BMI before pregnancy and smoking during pregnancy) and the child (birthweight) (Table 3). Linear regression models were performed to assess the ability of RWG to predict BAz, FMI, FFMI at 7 years of age adjusting by birthweight classification, maternal BMI and smoking during pregnancy. Given that multiple tests with the same samples were performed, and in order to decrease the risk of type 1 errors, Bonferroni correction for multiple testing was considered to reduce the familywise error rate. This yielded a two-tailed significance threshold of \( p < 0.017 \) \([(0.05)/3 = 0.017]\) (Table 4). All statistical analyses were performed using Statistical Package for the Social Sciences IBM SPSS for Windows Statistical Software version 26.0 Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. Statistical significance was set at \( p < 0.05 \).

**Results**

Characteristics of study participants (newborns, mothers and children at 7 years) are shown in. A total of 28.4%, 19.4% and 33.7% of the children gained weight rapidly from 0 to 6 m, 6 to 12 m and 0 to 12 m, respectively. Significant differences were observed between boys and girls in birthweight classification, rapid weight gain during the first year of life, height at 7 years, BAz status of children at 7 years, fat mass at 7 years and fat mass index at 7 years (\( p < 0.005 \)). The boy presented a significantly higher proportion of RWG between birth and 1 year of age, compared with girls Table 1.

Comparisons of means of body composition outcomes at 7 years (BAz, FMI and FFMI) according to the presence of RWG from 0 to 6 m, 6 to 12 m and 0 to 12 m are shown in Children showing RWG from 0 to 6 m, 6 to 12 m
Table 1. Sociodemographic characteristics of the children and their mothers.

|                                | Total       | Boys        | Girls       | p - value |
|--------------------------------|-------------|-------------|-------------|-----------|
| **Gender (%)**                 |             |             |             |           |
| Male                           | 356 (53.1%) | 189 (53.1%) | 167 (46.9%) |           |
| Female                         |             |             |             |           |
| **Maternal education**         |             |             |             |           |
| <Elementary                    | 67 (33.8%)  | 33 (33.8%)  | 34 (33.8%)  | 0.64      |
| Elementary to secondary        | 124 (44.1%) | 66 (44.1%)  | 58 (44.1%)  |           |
| >Bachelor                      | 157 (44.1%) | 88 (44.1%)  | 69 (44.1%)  |           |
| **Perinatal characteristics from the newborn** | | | | |
| Birth weight (g)               | 3216 ±493.9 | 3253.75 ±511.0 | 3175.18 ±417.84 | 0.137 |
| Birthweight classification     | 25 (7.0%)   | 16 (8.5%)   | 9 (5.4%)    | 0.009    |
| Small n (%)                    | 224 (62.9%) | 105 (55.6%) | 119 (71.3%) |           |
| Adequate n (%)                 | 107 (30.1%) | 68 (36%)    | 39 (23.4%)  |           |
| Macrosomic n (%)               |             |             |             |           |
| Gestational age                | 25 (7.0%)   | 16 (8.5%)   | 9 (5.4%)    | 0.255    |
| Preterm n (%)                  | 318 (89.3%) | 166 (87.8%) | 152 (91.0%) |           |
| Term n (%)                     |             |             |             |           |
| Typo of feeding 0 – 4 mo       | 000         | 000         | 000         |           |
| Breast milk n (%)              |             |             |             |           |
| Mixed feeding n (%)            |             |             |             |           |
| Formula n (%)                  |             |             |             |           |
| Rapid Weight Gain              | 101 (28.4%) | 61 (32.3%)  | 40 (24%)    | 0.820    |
| 0 – 6 mo n (%)                 | 69 (19.4%)  | 46 (24.3%)  | 52 (31.1%)  | 0.325    |
| 6 – 12 mo n (%)                | 120 (33.7%) | 68 (36%)    | 23 (13.8%)  | 0.011    |
| 0 – 12 mo n (%)                |             |             |             |           |
| **Perinatal characteristics from the mother** | | | | |
| Maternal BMI before pregnancy  | 16 (4.5%)   | 9 (4.8%)    | 7 (4.2%)    | 0.901    |
| Underweight n (%)              | 222 (62.4%) | 116 (61.4%) | 106 (63.5%) |           |
| Normal weight n (%)            | 68 (19.1%)  | 38 (20.1%)  | 30 (18.0%)  |           |
| Overweight n (%)               | 35 (9.8%)   | 20 (10.6%)  | 15 (9.00)   |           |
| Obesity n (%)                  |             |             |             |           |
| Weight gain during pregnancy   | 138 (39.9%) | 70 (37.4%)  | 68 (42.8%)  | 0.248    |
| Insufficient n (%)             | 130 (37.6%) | 68 (36.4%)  | 62 (39.0%)  |           |
| Adequate n (%)                 | 78 (22.5%)  | 49 (26.2%)  | 29 (18.2%)  |           |
| Excessive (%)                  |             |             |             |           |
| Smoking during pregnancy       | 65 (18.3%)  | 37 (19.6%)  | 28 (16.8%)  | 0.493    |
| Yes n (%)                      | 291 (81.7%) | 152 (80.4%) | 139 (83.2%) |           |
| No n (%)                       |             |             |             |           |
| **Characteristics of children at 7y** | | | | |
| Height (m) m ± SD              | 1.26 ±0.058 | 1.27 ±0.058 | 1.25 ±0.058 | 0.026    |
| Weight (Kg) m ± SD             | 27.92 ±11.625 | 28.78 ±15.245 | 26.947 ± 4.89 | 0.137 |
| BMI (Kg/m²) m ± SD             | 17,13 ±2,36  | 17,15 ±2,39  | 17,10 ±2,33  | 0.838    |
| BMI Status                     | 212 (59.6)  | 111 (58.7)  | 101 (60.5)  | 0.007    |
| Normal-weight n (%)            | 88 (24.7%)  | 38 (20.1%)  | 50 (29.9)   |           |
| Overweight n (%)               | 56 (15.7%)  | 40 (21.2%)  | 16 (9.6)    |           |
| Obesity n (%)                  |             |             |             |           |
| BAz m ± SE                     | 0.81 ±1.19  | 0.87 ±0.09  | 0.75 ±0.08  | 0.354    |
| Fat mass (Kg) m ± SD           | 7.01 ±2.89  | 6.55±2.88   | 7.53±2.82   | 0.001    |
| FMI (Kg/m²) m ± SD             | 4.36 ±1.65  | 4.02±1.60   | 4.75±1.62   | 0.000    |
| Free fat mass (Kg) m ± SD      | 16.28 ±2.66 | 17.03±2.74  | 15.42±2.30  | 0.000    |
| FFM (Kg/m²) m ± SD             | 10.18 ±1.08 | 10.54±1.06  | 9.78±0.94   | 0.000    |

Abbreviations: GA, Gestational age; mo, months; y, years; BMI = Body mass index; BAz, body mass index, FMI = Fat mass index; Kg = Kilograms; m = meters; m ± SD = mean and standard deviation; SE = standard error. *Fat mass was determined by Dual-energy X-ray absorptiometry and values presented belong to subtotal body composition analysis. Statistically significant results are shown in bold font.
Table 2. Description of adiposity indicators according to rapid weight gain during the first year of life.

| RWG  | Boys | Girls | Total | Boys | Girls | Total | Boys | Girls | Total |
|------|------|-------|-------|------|-------|-------|------|-------|-------|
|      | Mean ± S.D (n) | p-value |
|      | BAZ  | FMI   | FFMI  | BAZ  | FMI   | FFMI  | BAZ  | FMI   | FFMI  |
| 0 – 6 m |      |       |       |      |       |       |      |       |       |
| Yes  | 1.09 ± 1.27 | 0.70 ± 0.76 | 0.91 ± 1.09 | 0.71 ± 0.73 | 0.87 ± 1.04 | 0.88 ± 1.09 | <0.05 | <0.05 | <0.05 |
| No   | 0.92 ± 0.70 | 0.71 ± 0.73 | 0.93 ± 1.09 | 0.71 ± 0.73 | 0.87 ± 1.04 | 0.88 ± 1.09 | <0.05 | <0.05 | <0.05 |
| 6 – 12 m |      |       |       |      |       |       |      |       |       |
| Yes  | 1.18 ± 1.14 | 0.65 ± 0.77 | 1.12 ± 1.14 | 0.71 ± 0.77 | 0.87 ± 1.14 | 0.88 ± 1.14 | <0.05 | <0.05 | <0.05 |
| No   | 1.01 ± 1.01 | 0.71 ± 0.77 | 1.03 ± 1.01 | 0.71 ± 0.77 | 0.87 ± 1.14 | 0.88 ± 1.14 | <0.05 | <0.05 | <0.05 |

Abbreviations: BAZ, Body mass index z-score; FMI, Fat mass index; FFMI, Free fat mass index; RWG, Rapid weight gain; Sem, semester; Y, year. Means parametric variables (BAZ) were compared by T-tests and means of nonparametric variables (FMI and FFMI) were compared by Mann-Whitney. Body composition was assessed by dual x-ray absorptiometry. RWG was defined as a positive change (≥0.67) in the weight for age Z-Score in the established periods.
**Table 3.** ANCOVA analysis. Adiposity indicators at 7y according to rapid weight gain in the first year of life in boys and girls.

| RWG     | Boys            | Girls          | Total              | Boys            | Girls          | Total              | Boys            | Girls          | Total              | p-value |
|---------|-----------------|----------------|--------------------|-----------------|----------------|--------------------|-----------------|----------------|--------------------|---------|
| 1<sup>st</sup> SEM | 1.37±0.17(60)  | 1.01±0.19(40)  | 1.24±0.13(100)     | 4.40±0.22(60)   | 4.71±0.28(40)   | 4.50±0.18(100)     | 11.00±0.14(60) | 9.97±0.16(40)  | 10.62±0.11(100) | p=0.001 |
| Yes     | 0.64±0.11(127)  | 0.62±0.10(120) | 0.63±0.08(247)     | 3.86±0.15(127)  | 4.71±0.15(120)  | 4.28±0.11(247)     | 10.34±0.09(127) | 9.68±0.09(120) | 10.00±0.07(247) | p=0.085 |
| No      | p=0.001         | p=0.085        | p=0.000            | p=0.054         | p=0.997        | p=0.322            | p=0.000         | p=0.124        | p=0.000            |         |
| 2<sup>nd</sup> SEM | 1.17±0.19(46)  | 1.31±0.23(22)  | 1.22±0.14(68)      | 4.35±0.24(46)   | 5.81±0.33(22)   | 4.84±0.20(68)      | 10.85±0.15(46) | 9.97±0.20(22)  | 10.56±0.13(68) | p=0.075 |
| Yes     | 0.78±0.11(135)  | 0.63±0.09(134) | 0.70±0.07(269)     | 3.95±0.14(135)  | 4.55±0.13(134)  | 4.25±0.10(269)     | 10.43±0.09(135) | 9.71±0.08(134) | 10.07±0.06(269) | p=0.006 |
| No      | p=0.075         | p=0.006        | p=0.001            | p=0.149         | p=0.001        | p=0.008            | p=0.021         | p=0.228        | p=0.001            |         |
| 1<sup>st</sup> Y | 1.27±0.17(67)  | 1.13±0.17(51)  | 1.23±0.12(118)     | 4.43±0.21(67)   | 5.03±0.26(51)   | 4.69±0.17(118)     | 10.90±0.14(67) | 10.00±0.15(51) | 10.55±0.11(118) | p=0.024 |
| Yes     | 0.64±0.12(114)  | 0.53±0.11(105) | 0.58±0.08(219)     | 3.83±0.16(114)  | 4.58±0.17(105)  | 4.19±0.12(219)     | 10.33±0.10(114) | 9.62±0.10(105) | 9.97±0.07(219)  | p=0.049 |
| No      | p=0.005         | p=0.007        | p=0.000            | p=0.035         | p=0.175        | p=0.024            | p=0.001         | p=0.049        | p=0.000            |         |

Abbreviations: BAZ, Body mass index z-score; FMI, Fat mass index; FFMI, Free fat mass index; S.E, standard error. RWG, Rapid weight gain; Sem, semester. Body composition was assessed by dual x-ray absorptiometry. RWG was defined as a positive change (≥0.67) in the weight for age Z-Score in the established periods. Analysis were adjusted by birth weight, matenal BMI before pregnancy and smoking during pregnancy. Significant mean differences are shown in bold.
Table 4. Rapid weight gain as a predictor of body mass index, fat mass index and fat-free mass index. Results from adjusted linear regression models.

|     | Adj. R² | B     | CI               | p-value | p-value* |
|-----|---------|-------|------------------|---------|----------|
| BAZ | RWG from 0-6m in boys | 0.111 | 0.734 | [0.303; 1.165] | 0.001 | *          |
|     | RWG from 0-6m in girls | 0.012 | 0.381 | [-0.054; 0.816] | N.S | -          |
|     | RWG from 0-6m in all children | 0.071 | 0.607 | [0.303; 0.912] | 0.000 | *          |
|     | RWG from 6-12m in boys | 0.074 | 0.391 | [-0.039; 0.822] | N.S | -          |
|     | RWG from 6-12m in girls | 0.042 | 0.678 | [-0.658; 0.656] | 0.006 | *          |
|     | RWG from 6-12m in all children | 0.061 | 0.522 | [0.207; 0.837] | 0.001 | *          |
|     | RWG from 0-12m in boys | 0.099 | 0.631 | [0.194; 1.068] | 0.005 | *          |
|     | RWG from 0-12m in girls | 0.040 | 0.599 | [0.168; 1.029] | 0.007 | *          |
|     | RWG from 0-12m in all children | 0.079 | 0.649 | [0.345; 0.953] | 0.000 | *          |
| FMI | RWG from 0-6m in boys | 0.057 | 0.538 | [0.010; 1.087] | N.S | -          |
|     | RWG from 0-6m in girls | 0.010 | -0.001 | [-0.658; 0.656] | N.S | -          |
|     | RWG from 0-6 in all children | 0.012 | 0.217 | [-0.213; 0.646] | N.S | -          |
|     | RWG from 6-12m in boys | 0.051 | 0.395 | [-0.143; 0.932] | N.S | -          |
|     | RWG from 6-12m in girls | 0.085 | 1.259 | [0.552; 1.965] | 0.001 | *          |
|     | RWG from 6-12m in all children | 0.029 | 0.590 | [0.153; 1.026] | 0.008 | *          |
|     | RWG from 0-12m in boys | 0.064 | 0.593 | [0.043; 1.142] | 0.035 | N.S        |
|     | RWG from 0-12m in girls | 0.022 | 0.452 | [-0.203; 1.108] | N.S | -          |
| FFMI | RWG from 0-12m in all children | 0.024 | 0.493 | [0.065; 0.920] | 0.024 | N.S        |
|     | RWG during the 1st SEM in boys | 0.120 | 0.657 | [0.306; 1.007] | 0.000 | *          |
|     | RWG during the 1st SEM in girls | 0.053 | 0.297 | [-0.083; 0.677] | N.S | -          |
|     | RWG during the 1st SEM in all | 0.120 | 0.618 | [0.350; 0.887] | 0.000 | *          |
|     | RWG during the 2nd SEM in boys | 0.085 | 0.411 | [0.062; 0.760] | 0.021 | N.S        |
|     | RWG during the 2nd SEM in girls | 0.049 | 0.261 | [-0.165; 0.686] | N.S | -          |
|     | RWG during the 2nd SEM in all | 0.102 | 0.468 | [0.028; 0.763] | 0.001 | *          |
|     | RWG during the 3rd Y in boys | 0.109 | 0.579 | [0.225; 0.933] | 0.001 | *          |
|     | RWG during the 3rd Y in girls | 0.064 | 0.380 | [0.001; 0.758] | 0.049 | N.S        |
|     | RWG during the 3rd Y in all | 0.117 | 0.575 | [0.306; 0.843] | 0.000 | *          |

Linear regressions were performed separately adjusting by birthweight, maternal BMI before pregnancy and smoking during pregnancy. Sample Size for RWG 0-6 = 347, Sample size for RWG 6-12 and RWG 0-12 = 337. Abbreviations: RWG, Rapid Weight Gain; BMI, Body Mass Index; FMI, Fat Mass Index; FFMI, Free Fat Mass Index; 1st SEM, First Semester of life, 2nd SEM, Second Semester of life, 1st Y, First Year of life; β, Unstandardized coefficient; CI, Confidence Interval, N.S = Not significant, * = significant. RWG was defined as a positive change (>0.67) in the weight for age Z-Score in the established periods. Significant associations are shown in bold. p-value* = Significant p-values after Bonferroni correction, considered when p<0.017.

and 0 to 12 m had significantly higher BAZ compared with those that did not show RWG during these periods (p < 0.04 in all cases). When analyzed by sex, girls with RWG from 6 to 12 m were the only ones that present significantly higher BAZ than those without RWG (p = 0.005). Similar results were found for the FMI, given that only girls that developed RWG from 0 to 6 m (p = 0.000) and from 0 to 12 m (p = 0.024) presented significantly higher FMI than does who did not. Boys did not present significant mean differences in BAZ nor in FMI at any of the assessed periods. Regarding FFMI, significant differences were only observed in boys showing RWG from 6 to 12 m (p = 0.006) Table 2.

ANCOVA analyses adjusting by birthweight, maternal BMI and smoking during pregnancy are presented in Table 3. Children that present RWG 0–6 m, 6–12 m and 0–12 m presented higher BAZ at 7 years (p ≤ 0.001 in all cases). Differences between boys and girls were found in those with RWG
from 0 to 6 m, where only boys presented significative differences in BAZ (p = 0.001) and in those with RWG from 6 to 12 m, where only girls presented significative differences in BAZ (p = 0.006). Regarding FMI, children with RWG from 6 to 12 m and form 0–12 m presented significantly higher values of FMI (p = 0.008 and p = 0.024, respectively) and stratifying by sex, differences were found only in girls with RWG from 0 to 6 m (p = 0.001) and boys with RWG 6–12 m (p = 0.035). FFMI was higher in all children with RWG from 0 to 6 m, 6 to 12 m and 0 to 12 m (p ≤ 0.001 in all cases). Stratifying by sex, differences in FFMI were found only in boys with RWG from 0 to 6 m (p = 0.000) and from 6 to 12 m (p = 0.021). Both, boys and girls with RWG from 0 to 12 m presented higher FFMI at 7 years (p = 0.001 and p = 0.049, respectively).

Results from adjusted linear regression models were performed to assess body composition outcomes (BAZ, FMI and FFMI) according to RWG from 0 to 6 m, 0 to 12 m and 0 to 12 m. Results stratified by sex are presented in Table 4. RWG from 0 to 6 m, 6 to 12 m and 0 to 12 m was associated with BAZ in all children (B = 0.607, B = 0.522 and B = 0.649, respectively, p ≤ 0.001 in all cases). This can be interpreted as follows: children in the RWG from 0 to 6 m group have a 0.607 higher z-score than those in the non-RWG group. Specifically, only boys with RWG from 0 to 6 m presented a significative association with BAZ at 7y and only girls with RWG from 6 to 12 m presented a significative association with BAZ at 7y. Both, boys and girls presented positive associations between RWG from 0 to 12 m and BAZ at 7y.

Regarding FMI, no associations between RWG from 0 to 6 m were observed. However, positive significant associations were observed in all children that developed RWG 6–12 m (B = 0.590, p = 0.008), but only in girls (B = 1.259, p = 0.001). RWG from 0 to 12 m in all children was associated with higher FMI (B = 0.493, p = 0.024), but this was only seen in boys (B = 0.593, p = 0.035) and not in girls (B = 0.452, p > 0.05).

RWG from 0 to 6 m, 6 to 12 m and 0 to 12 m was positively associated with FFMI in all children (p ≤ 0.001 in all cases). Specifically, it was only associated with RWG from 0 to 6 m and from 6 to 12 m only in boys (B = 0.657, p = 0.000 and B = 0.411, p = 0.021, respectively). Regarding RWG from 0 to 12, positive associations were observed in boys (B = 0.579, p = 0.001) and girls (B = 0.380, p = 0.049).

After Bonferroni correction (Significance set at p < 0.017), most p-values remain significant, except for the associations between RWG from 0 to 12 m and FMI in boys, RWG from 6 to 12 m and FFMI in boys and RWG from 0 to 12 and FFMI in girls. These corrected results indicate that FMI is not longer associated with RWG in boys, but it remains significant in girls, and that FFMI remains significant in boys with RWG from 0 to 6 and from 0 to
12 but not from 6 to 12. Also, the only period in which RWG (0–12 m) was associated with FFMI in girls appeared to be no longer significant.

**Discussion**

The present study investigates the associations between RWG during three different periods of the first year of life and weight and adiposity outcomes including BAZ, FMI and FFMI at 7 years of age, in boys and girls from Aragón – Spain. To the authors’ knowledge, this study is the first to assess the relationship of RWG with FMI and FFMI as weight status indicators in Spain.

Along with our results, a strong body of evidence in previous studies have found that RWG during infancy and early childhood were associated with increased body fat deposition indices later in life. Rapid infant weight gain in from 0 to 12 m was previously identified as a predictor of overweight and obesity in the CALINA population at 6 years of age (Iguacel et al. 2018). These results are consistent with the ones obtained in the present study, because we have also found that RWG predicts BAZ at age 7 years. Later in life, this association is also preserved as other studies have also found positive associations between RWG and BMI at 9–10 years (Koontz et al. 2014; Zhou et al. 2016) and 17 years (Ekelund et al. 2006).

In this study, RWG from 6 to 12 m was associated with higher FMI in boys and girls. These results agree with previous studies that have assessed FMI and other fat mass indicators. For example, Nanri et al. showed that RWG in infancy (birth to 1.5 and 3 years) was associated with increased, percentage of body fat, waist circumference and waist to hip ratio at age 9 to 10 (Zhou et al. 2016). Ekelund et al. observed that RWG during infancy and early childhood was associated with larger FM, relative FM, and waist circumference at 17 years (Ekelund et al. 2006). A similar study performed in girls from the United Kingdom found that RWG between birth and 2 months and from 2 to 9 months was positively and significantly associated with increased body fat mass assessed by DXA (Ong et al. 2009).

Sex-specific differences in body composition were observed between boys and girls. At 7 years, boys presented significantly higher height and free fat mass than girls and girls presented a higher fat mass than boys. These findings go in line with previous studies that state that there are phenotypic differences in prepubertal children, e.g. girls tend to have higher total fat mass since 5 years of age compared to boys (Shaw et al. 2007; Guo et al. 2016) and different patterns of fat distribution, being girls characterized for having greater gynoid fat than boys (He et al. 2020).

It has been proposed that monitoring growth trajectories may improve nutrition-related chronic disease prevention (Péneau et al. 2017). Low birthweight has been identified as a nonmodifiable associated with RWG
(Mihrshahi et al. 2011), this is why all children with low weight at birth should be considered as a population at risk of developing RWG during the first years of life. Our study analyzed body composition at a young age, but it has to be acknowledged that these associations may remain until middle adulthood, as the study of Demerath et al. (2009) revealed that RWG from 0 to 2 years was associated with visceral, abdominal subcutaneous and total adiposity measured with dual-energy X-ray absorptiometry in middle adulthood (mean age 46.5 years). Another important factor that we should consider for the interpretation of these results is the fact that newborns with low birthweight may develop an early adiposity rebound which corresponds to the second rise in BMI curve that occurs between ages 5 and 7 years (Rolland-Cachera et al. 2005). Nevertheless, larger newborns should also be monitored given that in a previous study large-for-gestational-age children with RWG were those with higher BMI trajectories (Lu et al. 2020).

Determinants of RWG have been studied and given that they are associated with infant feeding and infant feeding practices like the use of high-protein formula, feeding to schedule and differences in feeding styles (Mihrshahi et al. 2011), interventions should focus on trying to improve nutritional aspects of the first months of life. In this sense, environmental interventions aiming to address obesity risk factors during early childhood may be especially useful in children with RWG at any period of the first year of life. Multicomponent interventions targeting feeding, and parenting styles, especially responsive the parenting style; diet including breastfeeding because its high-fat, low protein content may be beneficial for growth processes (Rolland-Cachera et al. 2005), healthy complementary feeding and healthy snacking; and physical activity, including the avoidance of sedentary behaviours in older preschool children, have shown some success in reducing obesity risk (Lanigan 2018).

Even though we have evaluated potential perinatal covariates, factors that may also play an important role including dietary intake (Nguyen et al. 2020), eating behaviours (Abdella et al. 2019), parental feeding practices (Vaughn et al. 2016), and physical activity levels or compliance of current recommendations (Growth 2018) were not assessed.

Our results suggest that an important key message for health-care professionals that could be helpful in their clinical practise would be to accurately address lifestyle behaviours including dietary intake, physical activity and sleep during growth, especially in children that had developed rapid weight gain during the first years of life.
**Strengths of this study**

A strength of the present study was the inclusion of body composition indicators obtained by DXA, which is an accurate method for body composition assessment (Colley et al. 2015). Another strength is that all measurements were performed by the same-trained researchers, which is positive in terms of inter reliability of measurements.

**Limitations of this study**

Some limitations should also be acknowledged. Even though the CALINA study is a representative study of the region of Aragón, results might not be extrapolated to the whole Spanish population, given the fact that the sample size is smaller, compared to the baseline CALINA study; fortunately, efforts were made in order to contact as many participants as possible, but some of them had moved from Zaragoza or were unreachable by phone.

**Conclusion and clinical implications**

In conclusion, this study suggests that RWG is associated with higher BAZ and FFMI in 7-year-old children but also with FMI, which indicates that these children are not only bigger but also have a higher fat mass than those without RWG. These results favour the use of such indexes as FMI and FFMI in the assessment of the healthy child in order to properly address potential effects of RWG during childhood, therefore we encourage health-care professionals to assess body composition indicators. Future studies could identify risk factors for developing RWG in order to develop interventions to prevent its course and potential interventions to prevent long-term effects of rapid weight gain.

**Acknowledgments**

The authors thank the families that participated in this study. The authors have no conflicts of interest to disclose. F-B. P. was funded by a grant from the Aragon Regional Government from Spain (Diputación General del Gobierno de Aragón, DGA). The authors thank the CALINA participants and their parents who volunteered and took part in this project. Crecimiento y Alimentación durante la Lactancia y la primera Infancia en Niños Aragoneses (CALINA) Collaborative Group. Instituto de Investigación Sanitaria (Institute of Health Research), Aragón.

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Disclosure statement

No, potential conflict of interest was reported by the authors.

Funding

This work was supported by the Diputación del Gobierno de Aragón (DGA) [-].

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