Journal of Translational Medicine

RESEARCH

Open Access

Metabolic and inflammatory status in prepuberty and early adulthood for individuals with a history of extrauterine growth restriction: a cohort study

Laura Palomino-Fernández[1†], Inmaculada Velasco[2†], Belén Pastor-Villaescusa[1,3,6*], Katherine Flores-Rojas[1,5], María de la Cruz Rico[4], Juan Roa[2,5], Ángel Gil[4,5] and Mercedes Gil-Campos[1,5]

Abstract

Background Perinatal growth and nutrition have been shown to be determinants in the programming of different tissues, such as adipose tissue, predisposing individuals to metabolic alterations later in life. Previous studies have documented an increased risk of metabolic disturbances and low-grade inflammation in prepubertal children with a history of extrauterine growth restriction (EUGR). The aim of this study was to evaluate possible alterations resulting from impaired growth during early childhood and their impact on young adult health.

Methods This is a longitudinal, descriptive and analytical study of a cohort with a history of EUGR recruited at prepubertal age and followed up for 10 years until the end of puberty. Anthropometric measurements, blood pressure, biochemical parameters related to lipid and carbohydrate metabolism and plasma adipokines and cytokines were analyzed.

Results Compared with prepubertal children, young adults EUGR presented increased abdominal circumference percentiles. Moreover, insulin levels and the homeostatic model assessment for insulin resistance (HOMA-IR) index were higher in young adults, with a considerable proportion of participants (22%) becoming insulin-resistant after pubertal development. In contrast, arterial hypertension was observed in 36% of prepubertal children compared with 18% of postpubertal young adults. Lipid values were within normal ranges without differences. Adiponectin and leptin remained at similar levels in adulthood, with a decrease in resistin.

Conclusion Individuals with a history of EUGR have increased metabolic risk in adulthood, which emphasizes the importance of clinical follow-up from childhood to prevent the development of further future associated diseases.

Keywords Adipokines, Extrauterine growth restriction, Inflammation, Insulin resistance, Nutrition, Puberty

[†]Laura Palomino-Fernández and Inmaculada Velasco equally contributed and should be considered joint first authors.

*Correspondence:
Belén Pastor-Villaescusa
belen.pastor@imibic.org

Full list of author information is available at the end of the article

Background

Extrauterine growth restriction (EUGR) is a frequent comorbidity associated to prematurity. In the absence of consensus, some authors define EUGR as a weight developed below the 3rd percentile (3p) (or below the 10th percentile, 10p) at 36 weeks corrected gestational age (GA) and/or at the time of discharge [1–3]. The EUGR condition not only increases the risk of mortality in preterm newborns [4, 5] but also potentially increases the risk of both short- and long-term metabolic disorders [6, 7].

Nutritional status during critical development periods, such as the perinatal period, is crucial for proper metabolic programming later in life. Fetal growth restriction (FGR) [8, 9] along with accelerated neonatal weight gain after preterm birth (up to 3 months post-term) is associated with the development of cardiovascular diseases (CVDs) in early adulthood [10–12]. Similarly, EUGR has been associated with cardiometabolic risk [7, 13, 14] and with long-term neurodevelopmental impairment during infancy [5, 15–17].

Overall, prenatal and early postnatal nutrition has been extensively studied for its association with various factors that may influence the development of certain diseases or serve as protective agents. These factors include, among others, the programming of adipose tissue [18] and the gut microbiota [19]. This underscores the importance of early detection and management of EUGR in preterm infants, as this condition occurs in neonatal units and is potentially preventable through an early detection and individualized nutritional strategies. Furthermore, emerging research studies suggest that malnutrition during the early days of life may lead to the onset of various CVDs [20, 21]. However, the mechanisms underlying this link between early nutrition and cardiovascular health remain unclear.

Hemodynamic redistribution, cardiovascular remodeling, increased arterial thickness, perinatal inflammation, oxidative stress and altered adipogenesis in response to inadequate nutrition may all play a role in this early programming [7, 18, 22]. Alterations in adipokine profiles and a low-grade level of inflammation have been reported in children with a history of EUGR [6, 23]. The most metabolically relevant adipokines include adiponectin, resistin and leptin, which are secreted in response to changes in adipocyte glycerol storage and inflammation [24]. Moreover, overexpression of cytokines such as tumor necrosis factor α (TNF-α), C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-1β, monocyte chemotactic protein 1 (MCP-1) or plasminogen activator inhibitor-1 (PAI-1) contribute to the development of chronic or low-grade systemic inflammation [25]. Furthermore, recent studies conducted by our research group revealed that children with a history of EUGR exhibit an impaired antioxidant system enzyme profile [23, 26], elevated blood pressure (BP) [6, 7] and higher plasma levels of proinflammatory biomarkers compared with their preterm and term counterparts [7, 27], leading to an increased risk of CVDs.

In this context, the risk of developing metabolic pathologies during childhood and puberty in individuals with a history of EUGR highlights the need to monitor the transition of these patients into adulthood, since there is no literature about the evolution later in life. Therefore, the principal aim of the present study (BIORICA-10) was to compare the metabolic and inflammatory status of individuals with a history of EUGR at the prepubertal stage and after puberty as young adults. These findings will contribute to evaluating the risk of developing metabolic diseases associated with the EUGR condition during the transition from childhood to young adulthood.

Materials and methods

Study design

The present study was designed as a cohort study. Participants with a history of EUGR were evaluated during their prepubertal age and in their young adulthood stage. The inclusion criterion for the EUGR group was a perinatal weight below the 3p at 36 weeks corrected GA and/or at the time of home discharge, to be more restrictive [1–3]. The exclusion criteria included neonatal pathologies not associated with the EUGR condition or any actual pathology that could alter lipid or carbohydrate profiles or inflammation status.

Analyses were conducted at two different time points: prepuberty and after the pubertal stage was concluded. Participants with a history of EUGR were recruited at pubertal Tanner stage I, without any metabolic disease that could influence the study results, and anthropometrics and hormonal analysis were assessed. These participants were re-evaluated after puberty, 10 years after the first evaluation. Of the initial 38 EUGR participants [6, 23], five lacked data at one of the two time points. Therefore, the final number of participants included in the study was 33.

Clinical history, physical examination, and anthropometric and blood pressure measurements

Perinatal clinical data, along with personal and family health records, were collected from the individuals clinical history, as previously published [6, 23]. No significant family disease history among the participants warranted exclusion from our analysis. An extended physical exploration was conducted in all participants by the research physician. Pubertal status was established on the basis of Tanner stages and confirmed by sex hormone analyses. Body weight, height and waist circumference (WC) were measured according to standardized procedures, with

the participants in minimal clothing, barefoot and fasted overnight. Body weight, height and WC percentiles were calculated using representative Spanish tables stratified by age and sex [28–30]. With respect to WC, percentiles are available from age 5 onward. Height and body weight were categorized into 3 percentiles blocks: <25p, 26-75p, and >75p. To estimate abdominal fat, WC was measured because it correlates adequately with intra-abdominal fat [31, 32]. WC was categorized into 2 blocks: Participants with <90p were classified as having a normal WC whereas those with ≥90p were considered to have abdominal fat [33, 34]. For all percentiles, participants older than 18 years were assigned the values established for 18-year-olds, as growth and development are considered complete by this age. Furthermore, body mass index (BMI, kg/m^2) and BMI z score were calculated for all participants using the standard growth percentile charts for the Spanish population [29]. Overweight and obesity were defined as BMI z scores ≥1 and ≥2, respectively, in participants under 18 years old and BMI ≥25 and 30 kg/m^2 in those older than 18 years [35]. Moreover, they were classified as underweight and/or short stature if their percentiles were below 3p [36].

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice by the same observer with a Dinamap V-100. The participants rested in the supine position for ≥5 min, and a correct cuff was placed around the left arm. For participants under 18 years of age, BP percentiles were established according to age and sex; high BP (HBP) was defined as BP levels >95p. In participants older than 18 years, HBP was defined as values ≥140/90 mmHg according to the European Society of Cardiology/European Society of Hypertension Guide from 2018 [37].

Dietary habits

Dietary intake across the two life stages was assessed using a semiquantitative food frequency questionnaire, which included common foods consumed in Spain [38]. Individuals or caregivers (at the prepubertal stage) and the own participants (at the young adulthood stage) were interviewed by a trained dietician, and the consumption frequency of each food item in the last four weeks was recorded as never or hardly often (1–3 times per month; once, 2–4 or 5–6 times per week; and once, 2–3, 4–6 or >6 times per day). Food intake data were converted into daily food volume/weight (in ml or g) to calculate the Dietary Quality Index (DQI) validated for children [39] and adolescents [40] and to assess the adherence to Spanish dietary recommendations. This DQI is based on the food-based dietary guidelines, which aim to address nutritional requirements at the population level to promote a healthy lifestyle. The major components of this DQI are *dietary quality*, *dietary diversity* and *dietary equilibrium*. The detailed technical aspects of the DQI have been described in other sources [40, 41]. To compute the DQI, the percentages of each component were extracted and the mean of them was calculated, with higher scores reflecting higher dietary recommendation compliance. The score was calculated at both the prepubertal and young adult stages.

Plasma metabolic parameters, proinflammatory biomarkers and adipokines

Blood samples were collected from EUGR participants at the prepubertal and young adult stages after a 12-h overnight fasting period, while the participants were in a resting position lying down and using an indwelling venous line. The general biochemical parameters were determined within 2-h of blood collection and other aliquots were stored at − 80 °C until the analysis of cytokines and adipokines.

The general biochemical parameters were performed by standardized laboratory methods at the Reina Sofía University Hospital (Córdoba, Spain) using the Architect c16000 and i2000SR autoanalyzers (Abbott Diagnostics®, Abbot Laboratories, Madrid Spain). External and internal quality controls were performed according to the hospital protocols. A lipid profile including plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), triacylglycerols (TGs), apolipoprotein A and B, and markers of carbohydrate metabolism such as glucose and insulin were measured [42–44]. To define dyslipidemia, cutoffs on HDLc and TGs levels, which are components on the metabolic syndrome (MetS) definition were used. For children ≤18 years old, HDLc and TG percentiles were obtained to classify the lipidemia status following the criteria of Olza et al. (2011) and Rúperez et al. (2018) [45, 46]: impaired HDLc (low) ≤10p and hypertriglyceridemia ≥90p. Individuals over 18 years old were classified according to the adult ranges established for plasma levels: impaired HDLc (low) <40 mg/dl and hypertriglyceridemia >150 mg/dl [47]. To conduct these classifications, the ObMetrics platform was used (version 1.0, Granada, Spain) [48]. To determine insulin resistance, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated using the formula: insulin (mU/l) × glucose (mmol/l)/22.5. The cutoff point of HOMA-IR was considered 2.5 in the prepubertal stage [46] and 3.0 in young adults as suggested for the adult population [44].

Furthermore, selected inflammatory biomarkers were measured in the plasma. CRP levels were also quantified using the autoanalyzer Architect c16000 by turbidimetric immunoassay with latex particles. In addition, cytokines such as neural growth factor (NGF), IL-6, IL-8, IL-1β, MCP-1, TNF-α, and PAI-1 and adipokines such as leptin,

resistin and adiponectin were analyzed in duplicate on a Luminex 200 system with XMap technology (Luminex Corporation, Austin, TX, USA) using human monoclonal antibodies (Milliplex Map Kit, Millipore, Billerica, MA, USA). Assay reproducibility was tracked to ensure that the values obtained were reliable (inter- and intra-assay coefficient of variation < 10%).

Statistical analysis

Data are reported as counts and proportions for categorical variables and as the mean ± standard error (SE) for continuous variables. All continuous variables were tested for normality and outliers using Q−Q plots and histograms. Two CRP values (one for each evaluated period) identified as outliers (> Q3 + 1.5 x IQR) were removed, along with one IL-8 value from the young adulthood period. The prepubertal to postpubertal progression of body composition and cardiometabolic risk markers were analyzed using two approaches: (1) For comparison of quantitative data between periods, a general linear model for repeated measures (GLM-RM) was used, adjusting for initial age, sex and BMI (as appropriate). The mean and SE values adjusted from the models were extracted, along with the pairwise differences (Δ); (2) For categorical data, longitudinal differences were evaluated by linear mixed-effects (*lme*) models using the `nlme` package [49, 50]. To consider individual variations, a random effect for participants was included to account for repeated measures. *Time* was included as a fixed effect to capture the change in variables over the two time points. To visualize the progression of cardiometabolic status from the prepubertal to the postpubertal stage, *Sankey* plots were constructed using the `ggsankey`, `ggplot2` and `dplyr` R packages [51].

Pearson's correlation coefficient (r) was calculated to establish the relationships between cardiometabolic variables. A significant correlation was defined as a value of *r* greater than 0.300. For dietary habits, to evaluate whether the DQI differed between the prepubertal and postpubertal stages, a paired *t*-test was performed. Data analyses were conducted using the SPSS Statistics 25 software (IBM SPSS, Inc., IBM, New York. USA) for the GLM-RM, and R statistical package (4.3.2 version) for the *lme* models. The *P* value was considered significant at < 0.05.

Table 1 Variations of anthropometry, body composition, blood pressure and metabolic risk markers between pre-pubertal and young adult stages in subjects with a history of EUGR condition

	Child	Young Adult	Δ	*P*-value[a]
Age (years)	8.1 ± 3.1	16.2 ± 3		
Sex (M/F)	29/4	29/4		
Anthropometry, body composition and blood pressure				
Weight (Kg)	25.15 ± 1	52.67 ± 2.26	25.15 ± 1.95	**< 0.001**
Height (cm)	121.08 ± 1.08	158.86 ± 1.54	37.77 ± 1.33	< 0.001
BMI (Kg/m^2)	16.5 ± 0.46	20.69 ± 0.72	4.19 ± 0.64	**< 0.001**
BMI z score	-0.47 ± 0.18	-0.29 ± 0.2	0.19 ± 0.22	0.388
WC (cm)	58.3 ± 1.5	72.35 ± 1.9	14.1 ± 2.04	**< 0.001**
SBP (mmHg)	112.5 ± 2.2	120.9 ± 2.2	8.4 ± 2.4	**0.020**[b]
DBP (mmHg)	69.3 ± 5	69.5 ± 4	0.23 ± 2.5	0.920[b]
HR (lpm)	83.4 ± 2.9	76.6 ± 3.4	-6.9 ± 3.74	0.079[b]
Carbohydrate metabolism				
Glucose (mg/dl)	86.6 ± 1.5	87.2 ± 1.5	0.54 ± 0.97	0.785[b]
Insulin (μU/ml)	5.8 ± 0.5	10.6 ± 1.04	4.7 ± 1.05	**< 0.001**[b]
HOMA-IR	1.3 ± 0.1	2.3 ± 0.25	1.02 ± 0.26	**0.001**[b]
Lipid metabolism				
TG (mg/dl)	64.5 ± 3.7	60.5 ± 5.5	-3.99 ± 6.2	0.500[b]
TC (mg/dl)	162.2 ± 5.2	151.4 ± 4.4	-10.8 ± 3.6	**0.005**[b]
HDLc (mg/dl)	54.05 ± 2.16	58.6 ± 2.2	4.5 ± 2.1	**0.040**[b]
LDLc (mg/dl)	95.1 ± 4.5	80.8 ± 3.5	-14.3 ± 3.16	**< 0.001**[b]
Apo A (mg/dl)	142.6 ± 4	130.6 ± 4.3	-11.93 ± 5.9	0.052[b]
Apo B (mg/dl)	65.9 ± 2.7	58.8 ± 2.15	-7.1 ± 2.09	**0.002**[b]

Abbreviations: Apo, Apolipoprotein; BMI, body mass index; DBP, diastolic blood pressure; EUGR, extrauterine growth restriction; HDLc, High-density lipoprotein; HR, heart rate; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LDLc, Low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerols; WC, waist circumference.

Data expressed as mean values ± standard error (SE) and differences (Δ ± SE).

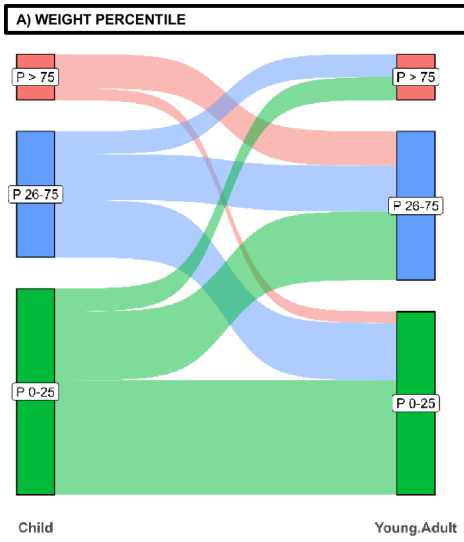
[a] General linear model for repeated measures (GLM-RM) adjusted for initial age, sex and BMI (as appropriate [b]). Significant P-value in bold.

Results

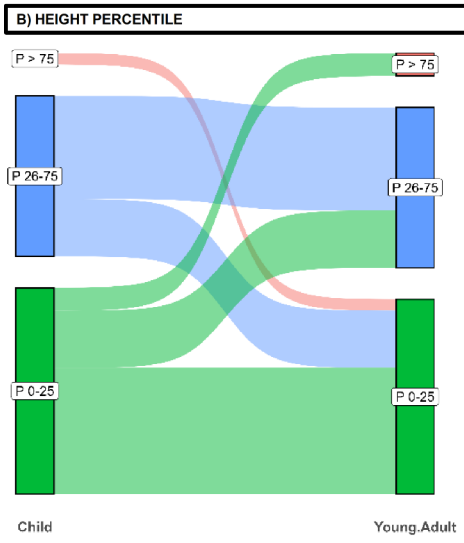
The prepubertal and postpubertal periods are referred in the present study as child and young adult groups, respectively. Some variations between the child and young adult stages were found regarding anthropometry, blood pressure and biochemical markers (Table 1). After puberty, the BMI of the study population was maintained within normal values. Among prepubertal children, 6% ($n = 2$) were underweight (weight < 3p) and 12% ($n = 4$) had short stature (height < 3p). In adulthood, these conditions increased to 15% ($n = 5$) for underweight and 18% ($n = 6$) for short stature.

Figure 1 shows the evolution of body weight (A) and height (B) between the two stages expressed as percentile ranges (< 25p, 26-75p, and > 75p). More than half of the children in the weight < 25p remained within this range after reaching puberty. Among the 4 children whose weight percentiles were > 75 during the prepubertal stage, the values decreased to lower percentiles (Fig. 1A). Similarly, for height, 61% of prepubertal children remained in < 25p in the postpubertal stage, with only 2 children moving to > 75p (Fig. 1B). Nevertheless, no significant differences were observed between the two periods in either weight or height percentiles (*lme* model $p = 0.711$ and $p = 0.640$, respectively).

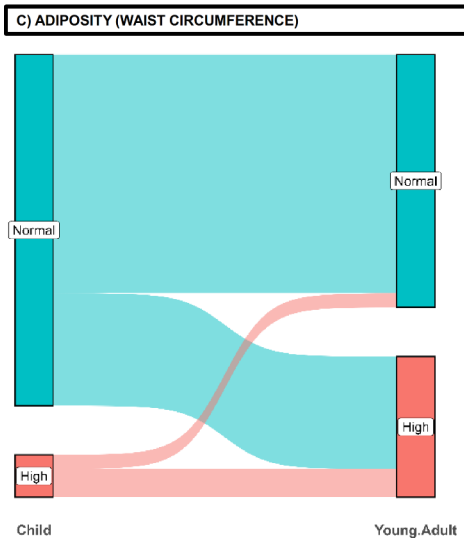
With respect to adiposity, the BMI z score remained unchanged across the two stages (Table 1). While only 3% of children were overweight ($n = 1$), this percentage raised to 18% in young adulthood ($n = 6$), with no significant differences in the evolution of weight status ($p = 0.865$). No



WEIGHT n (%)		Young Adult		
		< 25p	26-75p	> 75p
Child	< 25p	10 (55.6)	6 (33.3)	2 (11.1)
	26-75p	5 (45.5)	4 (36.4)	2 (18.2)
	> 75p	1 (25)	3 (75)	-



HEIGHT n (%)		Young Adult		
		< 25p	26-75p	> 75p
Child	< 25p	11 (61.1)	5 (27.8)	2 (11.1)
	26-75p	5 (35.7)	9 (64.3)	-
	> 75p	1 (100)	-	-



WC n (%)		Young Adult	
		High	Normal
Child	High	2 (67.7)	1 (33.3)
	Normal	17 (68)	8 (32)

Fig. 1 Evolution of anthropometric measurements in terms of percentile ranges of (**A**) weight and (**B**) height, and (**C**) adiposity status (waist circumference) between the prepubertal and young adult stages in participants with a history of EUGR condition. WC, waist circumference

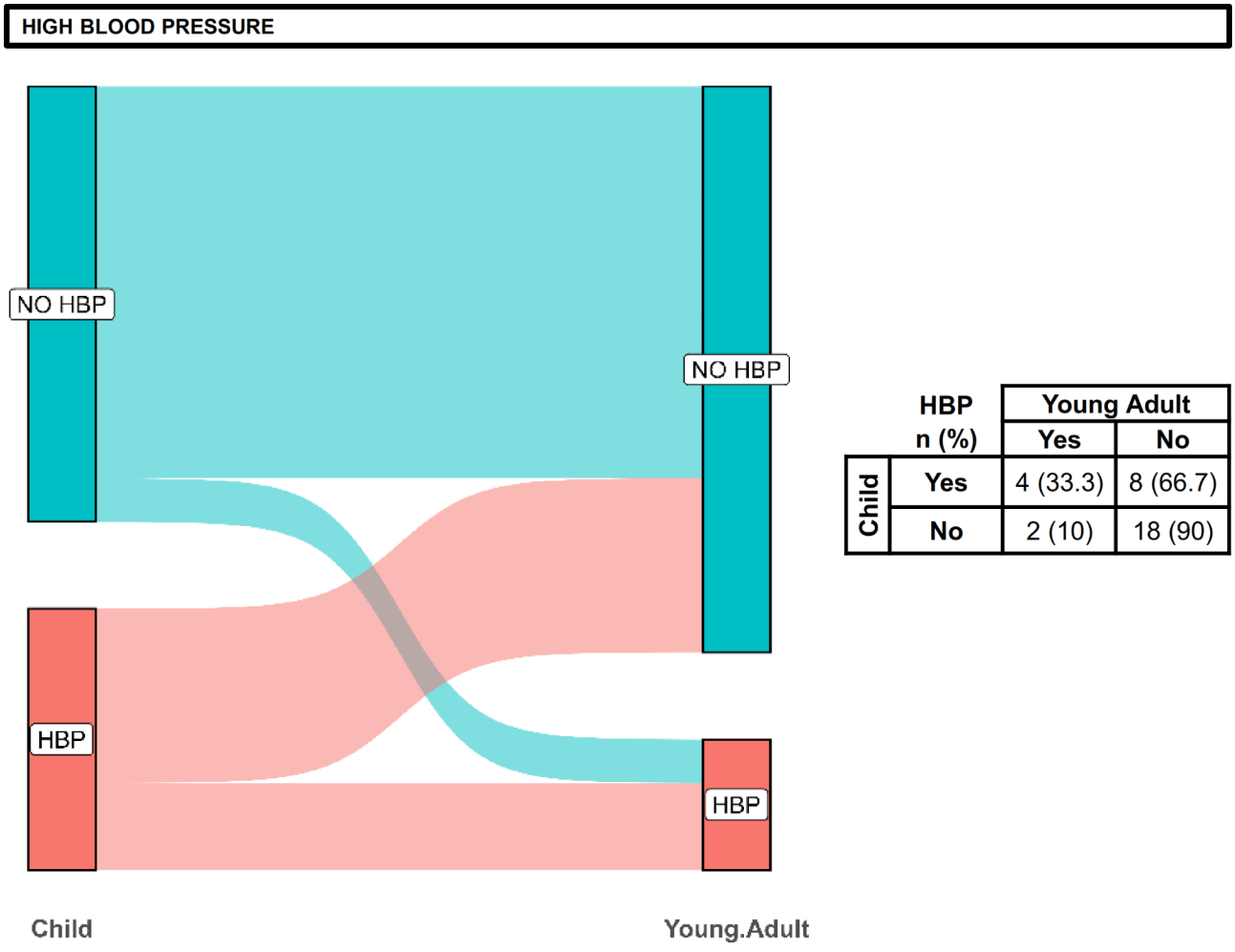
participants exhibited obesity at any time point during the study. Nevertheless, a significant increase in WC percentile was observed (Fig. 1C). In deep, 68% of the participants with a WC < 90p during childhood presented high abdominal adiposity (WC ≥ 90p) in early adulthood (*lme* model $p = 0.012$).

Among the children who had prepubertal HBP, 66.7% exhibited normal BP upon reaching puberty (*lme* model $p = 0.023$). Furthermore, 90% of those with normal BP during the prepubertal stage remained free of HBP after puberty (Fig. 2).

With respect to metabolic parameters, a significant increase were found in insulin and HOMA-IR levels from childhood to early adulthood (Table 1). As shown in Fig. 3A, a considerable proportion of participants became insulin resistant after pubertal development (*lme* model $p = 0.032$). In the lipid profile, the TC, LDLc and ApoB levels decreased while HDLc levels slightly increased in young adults compared with children (Table 1). However, when HDLc and TG were categorized to assess dyslipidemia, no significant differences were found (*lme* model $p = 0.161$ for HDLc and $p = 0.572$ for TG). Most of the participants presented a normal lipid profile (Fig. 3B and C), with only 2 children transitioning to hypertriglyceridemia in adulthood.

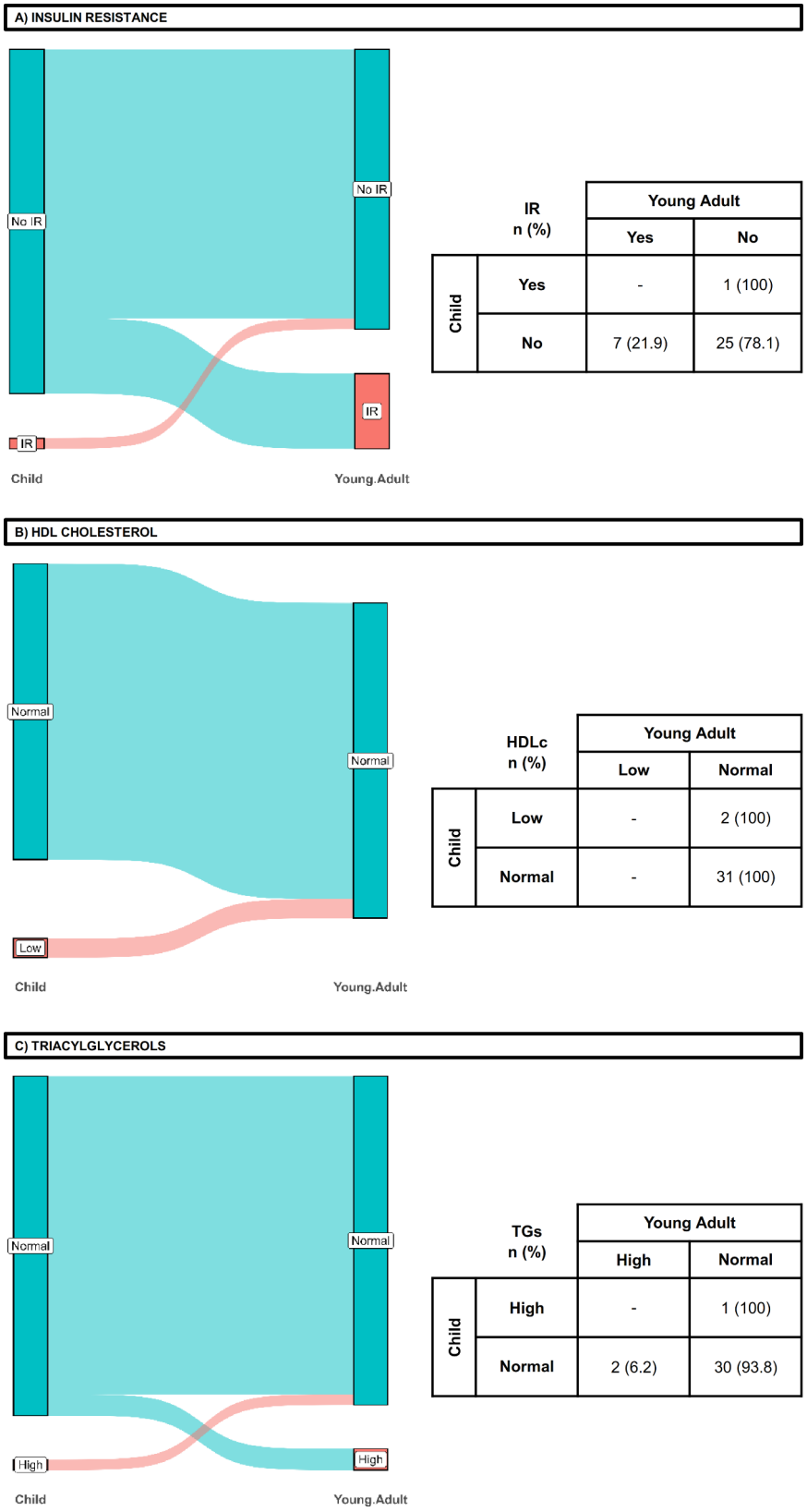
Furthermore, the paired t-test conducted for DQI revealed no differences between childhood and early adulthood ($p = 0.525$), maintaining intermediate dietary compliance in both stages (52 ± 9.5% vs. 50.4 ± 10.4%, respectively). Since no changes were observed in dietary habits, this variable was not included in the statistical models to avoid over-adjustments.

The changes in inflammation markers and adipokines are detailed in Table 2. For IL-6 and IL-1β, more than 50% of the values were out of the limit of sensitivity (0.2 pg/mL and 0.4 pg/mL, respectively), rendering these biomarkers inconclusive and thus excluded from analysis. Overall, a decrease in pro-inflammatory parameters such as the plasma levels of PAI-1, NGF, MCP-1, TNF-α and resistin, was observed upon reaching young adulthood.



	HBP n (%)	Young Adult	
		Yes	No
Child	Yes	4 (33.3)	8 (66.7)
	No	2 (10)	18 (90)

Fig. 2 Changes in the proportion of hypertension in participants with a history of EUGR from the prepubertal to postpubertal stage. HBP, high blood pressure



IR n (%)		Young Adult	
		Yes	No
Child	Yes	-	1 (100)
	No	7 (21.9)	25 (78.1)

HDLc n (%)		Young Adult	
		Low	Normal
Child	Low	-	2 (100)
	Normal	-	31 (100)

TGs n (%)		Young Adult	
		High	Normal
Child	High	-	1 (100)
	Normal	2 (6.2)	30 (93.8)

Fig. 3 Proportion of (**A**) insulin resistance, (**B**) HDLc and (**C**) triacylglycerols status from the prepubertal to young adult stage in participants with a history of EUGR. IR, insulin resistance; TGs, triacylglycerols

Table 2 Variations of cytokines and adipokines between prepubertal and young adult stages in participants with a history of EUGR

	Child	Young Adult	Δ	*P*-value[a]
PAI-1 (µg/l)	18.13 ± 1.33	14.3 ± 1.65	-3.8 ± 1.8	**0.045**
NGF (pg/ml)	8.9 ± 0.7	3.5 ± 0.3	-5.3 ± 0.6	**< 0.001**
MCP-1 (pg/ml)	189.5 ± 16.3	88.5 ± 5.8	-101.01 ± 14.1	**< 0.001**
TNF-α (pg/ml)	8.2 ± 0.3	1.7 ± 0.1	-6.5 ± 0.28	**< 0.001**
IL-8 (pg/ml)	2.71 ± 0.16	1.4 ± 0.19	-1.3 ± 0.28	**< 0.001**
CRP (mg/l)	1.47 ± 0.26	0.9 ± 0.28	-0.57 ± 0.42	0.180
Adiponectin (mg/l)	11.85 ± 1.25	14.67 ± 1.63	2.8 ± 1.5	0.060
Resistin (µg/l)	20.6 ± 1.3	13.5 ± 1.23	-7.09 ± 1.7	**< 0.001**
Leptin (µg/l)	7.6 ± 1.23	4.5 ± 0.74	-3.1 ± 1.6	0.055

Abbreviations: CRP, C-reactive protein; EUGR, extrauterine growth restriction; IL, interleukin; MCP-1, monocyte chemotactic protein type 1; NGF, neural growth factor; PAI-1, plasminogen activator inhibitor type 1; TNF-α, tumor necrosis factor-α.

Data expressed as mean values ± standard error (SE) and differences (Δ ± SE).

[a] General linear model for repeated measures (GLM-RM) adjusted for initial age, sex and BMI. Significant P-value in bold.

Table 3 Correlations among anthropometric and metabolic syndrome-related parameters in pre- pubertal and young adult stages in subjects with a history of EUGR

		Child		Young Adult	
		r	*P*-value	*r*	*P*-value
WC (p)	SBP	0.384	0.04	0.034	0.85
	HOMA-IR	0.28	0.149	0.394	**0.023**
	HDLc	0.018	0.926	-0.589	**< 0.001**
	TG	0.321	0.096	0.370	**0.034**
	Adiponectin	0.011	0.956	-0.378	**0.030**
	Leptin	0.741	**< 0.001**	0.573	**< 0.001**
SBP	HOMA-IR	0.397	**0.025**	0.175	0.07
	HDLc	0.305	0.090	-0.233	**0.015**
	Adiponectin	0.150	0.412	-0.310	**0.001**
HOMA-IR	TG	0.338	0.055	0.173	0.073
	Leptin	0.505	**0.003**	0.268	**0.007**
TG	HDLc	-0.259	0.145	-0.331	**< 0.001**
	Leptin	0.611	**< 0.001**	-0.04	0.68
HDLc	Adiponectin	0.463	**0.007**	0.393	**< 0.001**
	Leptin	0.054	0.765	0.303	0.472

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; EUGR, extrauterine growth restriction; HDLc, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDLc, low-density lipoprotein; SBP, systolic blood pressure; TG, triacylglycerols; WC (p), waist circumference percentile.

Data are expressed as Pearson correlation coefficient (r) and P-value. Significant P-value in bold.

Table 3 shows the relationships between cardiometabolic markers and the main adipokines. WC, expressed as percentiles, was directly correlated with HOMA-IR and TG only in young adulthood, but was directly correlated with leptin at both stages. Furthermore, WC was inversely correlated with adiponectin and HDLc in young adulthood. SBP was correlated with lower levels of HDLc and adiponectin in young adulthood and with higher HOMA-IR in childhood. HOMA-IR, in turn, was directly related to leptin levels at both stages, and HDLc levels were directly correlated with adiponectin.

Discussion

In recent years, EUGR has gained increasing importance because its association with complications later in life. Traditionally, postneonatal discharge complications are attributed primarily to prematurity. Progressively, consequences derived from this condition have been described, such as long-term neurodevelopmental alterations [52] and metabolic changes [7, 26]. In the present study, the evolution of different metabolic and inflammatory biomarkers was studied from childhood to adulthood in individuals with a history of EUGR. Given the clinical importance of preventing metabolic and CVDs in later life, early diagnosis and management of this growth retardation condition are essential for developing strategies to prevent associated complications.

In the present EUGR cohort, the percentages of underweight and underheight increased in the young adulthood. They were higher than the Spanish national value (5% for underweight and 2.5-3% for short stature) [36, 53, 54]. However, owing to the small sample size of our population, further studies are needed to confirm and extrapolate these results. Furthermore, it has been reported that the percentage of weight delay in EUGR (21%) is greater than that resulting in prematurity alone (6%) [7]. Interestingly, in our study, although approximately half of the participants had a body weight below 25p, showed a WC exceeding 90p in young adulthood, indicating abdominal obesity. These data also support the idea of changes in adipose tissue in individuals who are overnourished or undernourished under intrauterine or extrauterine conditions [13, 18, 22] and the need for an adequate nutritional status during the perinatal period to prevent the risk of metabolic comorbidities later in life. Therefore, health status, including adult life, should be followed up over time.

During childhood, these individuals were compared to a reference group of children born at term without complications [6, 23] showing higher BP levels, with nearly 50% reaching HBP [6]. However, after puberty, the percentage of individuals with hypertension decreased. Perhaps, these elevated SBP levels in prepubertal age may be overestimated due to the nervousness of children during BP measurement, even when standardized methods are used. On the other hand, high WC and BP levels have been traditionally related as reliable markers of MetS, as well as indicators of insulin resistance. In previous studies, the EUGR group during childhood displayed no relevant differences in insulin resistance compared with the reference group [6, 7]. However, this index increased in

adulthood similar to that of WC. Even when body weight is not high enough to affect other markers of cardiovascular risk, the most important associated and correlated factors are WC, SBP levels and HOMA-IR in pediatric populations [55–60]. Here, most of the classical features of MetS were correlated with WC.

The adipokine profile presented some changes in our population from childhood to adulthood. It has been reported that adiponectin, which has antithrombotic, antioxidant, anti-atherosclerotic and anti-inflammatory properties, is inversely associated with the risk of developing MetS [61, 62]. In addition, low adiponectin levels and high visceral adiposity are associated with hypertension, insulin resistance and β-cell dysfunction [63, 64]. Moreover, leptin is essential for maintaining energy balance and regulating body weight. Along with adiponectin, both play crucial roles in energy homeostasis, body weight regulation and metabolism [65]. Furthermore, the risk of MetS and abdominal obesity in people with high leptin levels, despite having a normal BMI, is well described [65, 66]. Although resistin is associated with obesity, some studies have reported inconsistent findings in relation to perinatal underweight and the regulation of insulin sensitivity and adipogenesis [67–69]. Hence, suppressed resistin levels, which act as insulin antagonists, have been reported in insulin resistance states [62]. In our study, we found that adiponectin and leptin values tended to significantly vary, and a decrease in resistin suggested an improvement in metabolic risk in adulthood. However, it must be considered that there are no reference values for normality and that these values may vary according to sex and age [70–73]. In our study, an inverse correlation between adiponectin levels and SBP and WC values was found in young adults. At both stages, we also found a direct relationship between leptin values and both WC and HOMA-IR. Leptin is a hormone produced directly by adipocytes in the white adipose tissue. Increased subcutaneous fat could lead to an increase in circulating leptin levels. Moreover, dysregulation of leptin signaling is linked to type 2 diabetes mellitus, a condition characterized by insulin resistance [74]. Nevertheless, further research should be conducted to elucidate the relationships between adipokines and EUGR.

With respect to the inflammatory profile, previous studies have suggested that prematurity, particularly EUGR, predisposes individuals to activate the inflammatory cascade [23, 75]. However, the effect of low-grade inflammation later in life is uncertain. In prepubertal children with a history of EUGR, higher plasma levels of some cytokines than in a reference group born at term without EUGR have been reported [26, 27]. However, during adulthood, we detected a decrease in TNF-α, IL-8 and MCP-1 plasma levels. In this context, the combination of IL-1β, IL-6 and TNF-α has been shown to have a growth inhibitory effect [76, 77]. Moreover, most of these inflammatory parameters and adipokines produced in adipose tissue may interfere with other multiple mechanisms of inflammation; therefore, the differences could be explained by an imbalance between pro-inflammatory and anti-inflammatory factors, which may stabilize after the completion of growth and puberty. However, it is unknown whether these alterations in the prepubertal individuals may lead to certain sequelae.

A paired analysis was performed to evaluate whether the DQI differed between the prepubertal and postpubertal stages [40] to control for the possible effects of the dietary habits on these results. In this context, individuals maintained an intermediate DQI across the life stages evaluated, and this situation could have positive effects on the evolution of some cytokines studied. Diet can influence the expression and secretion of biomarkers in different tissues, affecting the inflammatory status and modulating insulin resistance and endothelial dysfunction [78–80]. Several studies have demonstrated the link between specific types of diet and inflammatory markers associated to MetS, as well as how nutritional interventions can improve obesity-related inflammatory status [80–84].

The present study has several limitations. To date, there is no consensus on how postnatal growth should be defined and monitored in preterm infants, and the optimal growth pattern has not yet been determined in the perinatal stage [85, 86]. However, different definitions, some of which are stricter in defining EUGR, have been made on the basis of their relationship with the development of some comorbidities [87–90]. While this study presents some limitations due to the reduced simple size imposed by the strict criteria for early growth restriction applied in our cohort, it provides valuable insights into the long-term relationship between EUGR and associated comorbidities. Additionally, this work identifies key characteristics of postnatal growth patterns in this population that have not been previously described.

Conclusion

In conclusion, the present study stands out as the first to assess the metabolic profile of children with a history of EUGR on reaching adulthood. It attempts to clarify the translational importance of a correct follow-up of the metabolic components in these individuals. In adulthood, these individuals maintained growth retardation associated with abnormal fat distribution but there was no deterioration in adipokines or low-grade inflammatory status. However, it would be advisable to further study this population with prospective multicenter studies to clarify metabolic homeostasis and cardiovascular risk in the EUGR throughout different stages of life.

Abbreviations

Apo	Apolipoprotein
BMI	Body mass index
CRP	C-reactive protein
CVDs	Cardiovascular diseases
DBP	Diastolic blood pressure
DQI	Dietary quality index
EUGR	Extrauterine growth restriction
FGR	Fetal growth restriction
GA	Gestational age
GLM-RM	General linear model for repeated measures
HBP	High blood pressure
HDLc	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance
HR	Heart rate
IQR	Interquartile range
IL	Interleukin
LDLc	low-density lipoprotein cholesterol
lme	Linear mixed-effects
MCP-1	Monocyte chemotactic protein type 1
MetS	Metabolic syndrome
NGF	Neural growth factor
PAI-1	Plasminogen activator inhibitor type 1
SE	Standard error
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triacylglycerols
TNF-α	Tumor necrosis factor α
WC	Waist circumference

Acknowledgements
The authors would especially like to thank all the participants for their collaboration in the BIORICA-10 study. The authors gratefully acknowledge the support from the Consejería de Economía, Conocimiento, Empresas y Universidad, Junta de Andalucía, Spain (grant number PY18-1802), as well as the SPAOYEX Society for their research grant in the 2022 edition.

Author contributions
Laura Palomino-Fernández: Investigation, Methodology, Data curation, Formal analysis, Visualization, Writing original draft, Writing-review and editing; Inmaculada Velasco: Investigation, Methodology, Data curation, Writing original draft, Writing-review and editing, Supervision; Belén Pastor-Villaescusa: Investigation, Methodology, Data curation, Formal analysis, Visualization, Writing original draft, Writing-review and editing, Supervision; Katherine Flores: Investigation, Methodology, Data curation; María de la Cruz Rico: Methodology, Data curation, Writing-review and editing; Juan Roa: Conceptualization, Methodology, Writing-review and editing, Funding acquisition, Project administration, Resources, Supervision; Ángel Gil: Writing-review and editing; Mercedes Gil-Campos: Conceptualization, Investigation, Methodology, Writing original draft, Writing-review and editing, Funding acquisition, Project administration, Resources, Supervision.

Funding
This work was supported by the Modalidad Retos Consolidado. Dirección General de Investigación y Transferencia del Conocimiento. Consejería de Economía, Conocimiento, Empresas y Universidad. Junta de Andalucía, Spain (grant number PY18-1802). This work was partially funded by the SPAOYEX research grant 2022 edition.

Data availability
All data analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Hospital Ethical Committee (Córdoba, Spain; 20th February 2020; human ethics approval number 3729_2020). The selected individuals were informed, and signed consent was obtained. Participants under 18 years of age provided verbal consent, and written consent was signed by their parents or legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author details
[1]Metabolism and Investigation Unit, Maimonides Institute of Biomedicine Research of Córdoba (IMIBIC), Reina Sofia University Hospital, University of Córdoba, Córdoba, Spain
[2]Department of Cell Biology, Physiology and Immunology, University of Córdoba, Reina Sofia University Hospital, Maimonides Institute of Biomedicine Research of Córdoba (IMIBIC), Córdoba, Spain
[3]Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin (RICORS), Instituto de Salud Carlos III, Madrid RD21/0012/0008, Spain
[4]Department of Biochemistry and Molecular Biology II, School of Pharmacy, Institute of Nutrition and Food Technology "José Mataix", Biomedical Research Center, University of Granada, Instituto de Investigación Biosanitaria IBS, Granada, Spain
[5]Consorcio CIBER, M.P. Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[6]Metabolism and Investigation Unit, Reina Sofia University Hospital. IMIBIC, Av. Menéndez Pidal sn, Córdoba 14004, Spain

Received: 8 October 2024 / Accepted: 25 December 2024
Published online: 14 January 2025

References

1. Zozaya C, Díaz C, Saenz de Pipaón M. How should we define postnatal growth restriction in Preterm infants? Neonatology. 2018;114(2):177–80.
2. Izquierdo, Renau. Aldecoa-Bilbao, Esponera, Mendoza, Sanz, Iglesias-Platas. Applying methods for postnatal growth Assessment in the clinical setting: evaluation in a longitudinal cohort of very Preterm infants. Nutrients. 2019;11(11):2772.
3. Fenton TR, Chan HT, Madhu A, Griffin IJ, Hoyos A, Ziegler EE, et al. Preterm infant growth velocity calculations: a systematic review. Pediatrics. 2017;139(3):e20162045.
4. Martínez-Jiménez M, Gómez-García F, Gil-Campos M, Pérez-Navero J. Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review. Eur J Pediatr. 2020;179(8):1255–65.
5. Kim MS, Koh JW, Shin J, Kim SY. Postnatal growth Assessment and Prediction of Neurodevelopment and Long-Term growth in very low Birth Weight infants: a Nationwide Cohort Study in Korea. J Clin Med. 2024;13(10):2930.
6. Ortiz Espejo M, Gil Campos M, Muñoz Villanueva MC, Pérez Navero JL. Alteraciones metabólicas en prepúberes con retraso del crecimiento extrauterino. Pediatr (Engl Ed). 2012;77(4):247–53.
7. Ordóñez-Díaz MD, Pérez-Navero JL, Flores-Rojas K, Olza-Meneses J, Muñoz-Villanueva MC, Aguilera-García CM, et al. Prematurity with Extrauterine Growth Restriction increases the risk of higher levels of glucose, low-Grade of inflammation and hypertension in Prepubertal Children. Front Pediatr. 2020;8:180.
8. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
9. Colella M, Frérot A, Novais ARB, Baud O. Neonatal and long-term consequences of fetal growth restriction. Curr Pediatr Rev. 2018;14(4):212–8.
10. Kerkhof GF, Willemsen RH, Leunissen RWJ, Breukhoven PE, Hokken-Koelega ACS. Health Profile of Young adults born Preterm: negative effects of Rapid Weight Gain in Early Life. J Clin Endocrinol Metab. 2012;97(12):4498–506.
11. Chatmethakul T, Roghair RD. Risk of hypertension following perinatal adversity: IUGR and prematurity. JEndocrinol. 2019;242(1):T21–32.
12. de Mendonça ELSS, de Lima Macêna M, Bueno NB, de Oliveira ACM, Mello CS. Premature birth, low birth weight, small for gestational age and chronic non-communicable diseases in adult life: a systematic review with meta-analysis. Early Hum Dev. 2020;149:105154.

13. Moreno-Mendez E, Quintero-Fabian S, Fernandez-Mejia C, Lazo-De-La-Vega-Monroy ML. Early-life programming of adipose tissue. Nutr Res Rev. 2020;33(2):244–59.
14. Frithioff-Bøjsøe C, Lund MAV, Lausten-Thomsen U, Hedley PL, Pedersen O, Christiansen M, et al. Leptin, adiponectin, and their ratio as markers of insulin resistance and cardiometabolic risk in childhood obesity. Pediatr Diabetes. 2020;21(2):194–202.
15. González-López C, Solís-Sánchez G, Lareu-Vidal S, Mantecón-Fernández L, Ibáñez-Fernández A, Rubio-Granda A, et al. Variability in definitions and criteria of Extrauterine Growth Restriction and Its Association with neurodevelopmental outcomes in Preterm infants: a narrative review. Nutrients. 2024;16(7):968.
16. Strobel KM, Wood TR, Valentine GC, German KR, Gogcu S, Hendrixson DT, et al. Contemporary definitions of infant growth failure and neurodevelopmental and behavioral outcomes in extremely premature infants at two years of age. JPerinatol. 2024;44(6):811–8.
17. El Rafei R, Maier RF, Jarreau PH, Norman M, Barros H, Van Reempts P, et al. Postnatal growth restriction and neurodevelopment at 5 years of age: a European extremely preterm birth cohort study. Arch Dis Child Fetal Neonatal Ed. 2023;108(5):492–8.
18. Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, et al. The Power of Programming and the EarlyNutrition project: opportunities for health promotion by nutrition during the first thousand days of life and beyond. Ann Nutr Metab. 2014;64(3–4):187–96.
19. Abenavoli L, Scarpellini E, Colica C, Boccuto L, Salehi B, Sharifi-Rad J, et al. Gut microbiota and obesity: a role for Probiotics. Nutrients. 2019;11(11):2690.
20. Fan S, Zhang K, Lv A, Ma Y, Fang X, Zhang J. Characteristics of the intestinal microbiota and metabolism in infants with extrauterine growth restriction. Transl Pediatr. 2021;10(5):1259–70.
21. Duan J, Zhong Q, Luo L, Ning Y, Qi Z, Wang S et al. Metabolomic profiling of human feces and plasma from extrauterine growth restriction infants. Pediatr Res. 2024.
22. Koletzko B, Brands B, Grote V, Kirchberg FF, Prell C, Rzehak P, et al. Long-term Health Impact of Early Nutrition: the power of Programming. Ann Nutr Metab. 2017;70(3):161–9.
23. Ortiz-Espejo M, Gil-Campos M, Mesa MD, García-Rodríguez CE, Muñoz-Villanueva MC, Pérez-Navero JL. Alterations in the antioxidant defense system in prepubertal children with a history of extrauterine growth restriction. Eur J Nutr. 2014;53(2):607–15.
24. Farkhondeh T, Llorens S, Pourbagher-Shahri AM, Ashrafizadeh M, Talebi M, Shakibaei M, et al. An overview of the role of Adipokines in Cardiometabolic diseases. Molecules. 2020;25(21):5218.
25. Rana MN, Neeland IJ. Adipose tissue inflammation and Cardiovascular Disease: an update. Curr Diab Rep. 2022;22(1):27–37.
26. Ordóñez-Díaz MD, Gil-Campos M, Flores-Rojas K, Muñoz-Villanueva MC, Mesa MD, de la Torre-Aguilar MJ et al. Impaired antioxidant defence status is Associated with metabolic-inflammatory risk factors in Preterm Children with Extrauterine Growth Restriction: the BIORICA Cohort Study. Front Nutr. 202121;8:793862.
27. Ordóñez-Díaz MD, Gil-Campos M, Flores-Rojas K, Muñoz-Villanueva MC, Aguilera-García CM, de la Torre-Aguilar MJ et al. Plasma adipokines profile in prepubertal children with a history of prematurity or extrauterine growth restriction. Nutrients. 2020;12(4).
28. Sánchez González E, Carrascosa Lezcano A, Fernández García JM, Ferrández Longás A, López de Lara D, López-Siguero JP. Estudios españoles de crecimiento: situación actual, utilidad y recomendaciones de uso. Pediatr (Engl Ed). 2011;74(3):e1931–19316.
29. Carrascosa A, Fernández JM, Ferrández Á, Lopez JP, López D, Sanchez E et al. Estudios Españoles de Crecimiento 2010. 2010. Available from: https://www.seep.es/images/site/publicaciones/oficialesSEEP/Estudios_Espa%C3%B1oles_de_Crecimiento_2010.pdf
30. Moreno LA, Fleta J, Mur L, Rodriguez G, Sarria A, Bueno M. Waist circunference values in Spanish children -gender related differences. Eur J Clin Nutr. 1999;53(429):33.
31. Sarría A, Moreno L, García-Llop L, Fleta J, Morellón M, Bueno M. Body mass index, triceps skinfold and waist circumference in screening for adiposity in male children and adolescents. Acta Paediatr. 2001;90(4):387–92.
32. Sharp TA, Grunwald GK, Giltinan KEK, King DL, Jatkauskas CJ, Hill JO. Association of anthropometric measures with risk of diabetes and cardiovascular disease in hispanic and caucasian adolescents. Prev Med (Baltim). 2003;37(6):611–6.
33. Moreno L, Pineda I, Rodríguez G, Fleta J, Sarría A, Bueno M. Waist circumference for the screening of the metabolic syndrome in children. Acta Paediatr. 2002;91(12):1307–12.
34. Maffeis C, Pietrobelli A, Grezzani A, Provera S, Tatò L. Waist Circumference and Cardiovascular Risk factors in Prepubertal Children. Obes Res. 2001;9(3):179–87.
35. World Health Organization. Obesidad y sobrepeso, WHO., 2021.
36. González-Casado I, Guerrero-Fernández J. Manual de diagnóstico y terapéutica en endocrinología pediátrica V.1.1. 2020.
37. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.
38. Martin-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. Int J Epidemiol. 1993;22(3):512–9.
39. Huybrechts I, Vereecken C, De Bacquer D, Vandevijvere S, Van Oyen H, Maes L, et al. Reproducibility and validity of a diet quality index for children assessed using a FFQ. Br J Nutr. 2010;104(1):135–44.
40. Vyncke K, Cruz Fernandez E, Fajó-Pascual M, Cuenca-García M, De Keyzer W, Gonzalez-Gross M, et al. Validation of the Diet Quality Index for adolescents by comparison with biomarkers, nutrient and food intakes: the HELENA study. Br J Nutr. 2013;109(11):2067–78.
41. Huybrechts I, Vereecken C, Vyncke K, Maes L, Slimani N, De Henauw S. The 'Diet Quality Index' and its applications. Diet Quality. New York, NY: Springer New York; 2013. pp. 301–14.
42. García Cuartero B, García Lacalle C, Jiménez Lobo C, González Vergaz A, Calvo Rey C, Alcázar Villar MJ, et al. Índice HOMA Y QUICKI, insulina y péptido C en niños sanos. Puntos De corte de riesgo cardiovascular. Pediatr (Engl Ed). 2007;66(5):481–90.
43. Rogero Blanco ME, Albañil Ballesteros MR, Sánchez Martin M, Rabanal Basalo A, Olivas Domínguez A, García Lacalle C. Prevalencia De Resistencia a insulina en una población de jóvenes adultos. Relación con El estado Ponderal. Endocrinología Y Nutrición. 2012;59(2):98–104.
44. Masoodian SM, Omidifar A, Moradkhani S, Asiabanha M, Khoshmirsafa M. HOMA-IR mean values in healthy individuals: a population-based study in Iranian subjects. J Diabetes Metab Disord. 2022;22(1):219–24.
45. Olza J, Gil-Campos M, Leis R, Bueno G, Aguilera CM, Valle M, et al. Presence of the metabolic syndrome in obese children at Prepubertal Age. Ann Nutr Metab. 2011;58(4):343–50.
46. Rupérez AI, Olza J, Gil-Campos M, Leis R, Bueno G, Aguilera CM, et al. Cardiovascular risk biomarkers and metabolically unhealthy status in prepubertal children: comparison of definitions. Nutr Metab Cardiovasc Dis. 2018;28(5):524–30.
47. Expert Panel on Detection E and T of HBC in A. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
48. de BioNIT G. IC. Obmetrics. Bioinformatics Resources & Software. 2024. Available from: https://bionit.ugr.es/pages/investigacion/software/bioinformatics-methods-software)
49. Pinheiro JBDRCT, nlme. Linear and Nonlinear Mixed Effects Models. R package version 3.1–165. 2024.
50. Pinheiro JC, Bates DM. Mixed-effects models in S and S-PLUS. New York: Springer-; 2000.
51. Sjoberg D. Davidsjoberg/ggsankey: Sankey, Alluvial and Sankey Bump Plots. https://rdrr.io/github/davidsjoberg/ggsankey/
52. Belfort MB, Rifas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, Ryan P, et al. Infant growth before and after term: effects on Neurodevelopment in Preterm infants. Pediatrics. 2011;128(4):e899–906.
53. INE -. Instituto Nacional De Estadística. (n.d.). INE. National Institute of Statistics. Encuesta Nacional de Salud de España; 2020. https://ine.es/.
54. Aizpurua Galdeano P, Mateo Abad M, Alonso Alonso Á, Juaristi Irureta S, Carvajal Goikoetxea B, García Ruiz S, et al. Efecto Del cambio de gráficas de crecimiento de referencia en la prevalencia de talla baja. Pediatr (Engl Ed). 2020;92(1):28–36.
55. Genovesi S, Montelisciani L, Giussani M, Lieti G, Patti I, Orlando A, et al. Role of Insulin Resistance as a mediator of the relationship between Body Weight, Waist circumference, and systolic blood pressure in a Pediatric Population. Metabolites. 2023;13(3):327.
56. Cândido APC, Geloneze B, Calixto A, Vasques ACJ, Freitas RN, Freitas SN, et al. Adiponectin, HOMA-Adiponectin, HOMA-IR in children and adolescents: Ouro Preto Study. Indian J Pediatr. 2021;88(4):336–44.

57. Deusdará R, de Moura Souza A, Szklo M. Association between obesity, overweight, elevated Waist circumference, and insulin resistance markers among Brazilian adolescent students. Nutrients. 2022;14(17).
58. Sangrós FJ, Torrecilla J, Giráldez-García C, Carrillo L, Mancera J, Mur T, et al. Asociación De Obesidad general y abdominal con hipertensión, dislipemia y presencia de prediabetes en El estudio PREDAPS. Rev Esp Cardiol. 2018;71(3):170–7.
59. Hernández LM, Mazariegos M, Solomons NW. Relación entre circunferencia de cintura y presión arterial en mujeres guatemaltecas: El Estudio CRONOS. Revista Española De Nutrición Comunitaria. 2010;16(2):64–8.
60. Shen W, Punyanitya M, Chen J, Gallagher D, Albu J, Pi-Sunyer X, et al. Waist circumference correlates with metabolic syndrome indicators better than percentage Fat. Obesity. 2006;14(4):727–36.
61. Klünder-Klünder M, Flores-Huerta S, García-Macedo R, Peralta-Romero J, Cruz M. Adiponectin in eutrophic and obese children as a biomarker to predict metabolic syndrome and each of its components. BMC Public Health. 2013;13(1):88.
62. Liu Z, Liang S, Que S, Zhou L, Zheng S, Mardinoglu A. Meta-analysis of Adiponectin as a biomarker for the detection of metabolic syndrome. Front Physiol. 2018;9.
63. Palomer X, Pérez A, Blanco-Vaca F. Adiponectina: un nuevo nexo entre obesidad, resistencia a la insulina y enfermedad cardiovascular. Med Clin (Barc). 2005;124(10):388–95.
64. Moon HU, Ha KH, Han SJ, Kim HJ, Kim DJ. The Association of Adiponectin and Visceral Fat with insulin resistance and β-Cell dysfunction. J Korean Med Sci. 2018;34(1).
65. Haddawi KH, Al-Ziaydi AG, Al-Khalidi FAAK. The role of adipokines and ghrelin in interactions and clinical implications in childhood obesity. J Educ Health Promot. 2024;13(1).
66. Cheng J, Luo Y, Li Y, Zhang F, Zhang X, Zhou X, et al. Sex- and body mass index-specific reference intervals for serum leptin: a population based study in China. Nutr Metab (Lond). 2022;19(1):54.
67. Aknc A, Karakurt C, Gurbuz S, Elkran O, Nalbantoglu O, Kocak G, et al. Association of cardiac changes with serum adiponectin and resistin levels in obese and overweight children. J Cardiovasc Med. 2013;14(3):228–34.
68. Zamojska J, Niewiadomska-Jarosik K, Wosiak A, Gruca M, Smolewska E. Serum adipocytokines Profile in Children Born Small and Appropriate for Gestational Age—A comparative study. Nutrients. 2023;15(4):868.
69. Briana DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult disease: the role of adipocytokines. Eur J Endocrinol. 2009;160(3):337–47.
70. Pfützner A, Langenfeld M, Kunt T, Löbig M, Forst T. Evaluation of human resistin assays with serum from patients with type 2 diabetes and different degrees of insulin resistance. Clin Lab. 2003;49(11–12):571–6.
71. Gijón-Conde T, Graciani A, Guallar-Castillón P, Aguilera MT, Rodríguez-Artalejo F, Banegas JR. Leptin reference values and cutoffs for identifying Cardiometabolic abnormalities in the Spanish Population. Revista Española De Cardiología (English Edition). 2015;68(8):672–9.
72. Barrios V, Gómez-Huelgas R, Rodríguez R, de Pablos-Velasco P. Adiponectina, un factor de riesgo cardiovascular emergente. Estudio Ref Rev Esp Cardiol. 2008;61(11):1159–67.
73. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. Diabetologia. 2012;55(9):2319–26.
74. Meek T, Morton G. Leptin, diabetes, and the brain. Indian J Endocrinol Metab. 2012;16(9):534.
75. Nuyt AM, Lavoie JC, Mohamed I, Paquette K, Luu TM. Adult consequences of extremely Preterm Birth. Clin Perinatol. 2017;44(2):315–32.
76. Wong SC, Dobie R, Altowati MA, Werther GA, Farquharson C, Ahmed SF. Growth and the growth hormone-insulin like growth factor 1 Axis in Children with chronic inflammation: current evidence, gaps in knowledge, and future directions. Endocr Rev. 2016;37(1):62–110.
77. Choukair D, Hügel U, Sander A, Uhlmann L, Tönshoff B. Inhibition of IGF-I–related intracellular signaling pathways by proinflammatory cytokines in growth plate chondrocytes. Pediatr Res. 2014;76(3):245–51.
78. Hermsdorff HHM, Ángeles Zulet M, Bressan J, Alfredo Martínez J. Efecto De La dieta en la inflamación crónica y de bajo grado relacionada con la obesidad y El síndrome metabólico. Endocrinología Y Nutrición. 2008;55(9):409–19.
79. Esposito K, Nappo F, Giugliano F, Giugliano G, Marfella R, Giugliano D. Effect of dietary antioxidants on postprandial endothelial dysfunction induced by a high-fat meal in healthy subjects. Am J Clin Nutr. 2003;77(1):139–43.
80. Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr. 2004;79(6):969–73.
81. Podadera-Herreros A, Alcala-Diaz JF, Gutierrez-Mariscal FM, Jimenez-Torres J, Cruz-Ares S, de la, Arenas-de Larriva AP, et al. Long-term consumption of a mediterranean diet or a low-fat diet on kidney function in coronary heart disease patients: the CORDIOPREV randomized controlled trial. Clin Nutr. 2022;41(2):552–9.
82. Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, Quintana-Navarro GM, Fuentes F, Garcia-Rios A, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet. 2022;399(10338):1876–85.
83. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet supplemented with Extra-virgin Olive oil or nuts. N Engl J Med. 201821;378(25).
84. De Miguel-Etayo P, Jurado-Castro JM, Pérez-Ferreirós A, Flores K, Vázquez-Cobela R, Vucinic V. MEditerranean LIfestyle in Pediatric Obesity Prevention (MELI-POP). Revista Española De Nutrición Humana Y Dietética. 2020;24(1):12–3.
85. Ayala J, Romero L, Cuvi G, Monge J. Comparación de la utilidad clínica de datos antropométricos de recién nacidos prematuros empleando las gráficas Fenton E Intergrowth-21st / Comparison of the clinical utility of anthropometric data of preterm infants using Fenton and Intergrowth – 21 St charts. Rev Ecuat Pediatr. 2019;20(2).
86. Fenton TR, Cormack B, Goldberg D, Nasser R, Alshaikh B, Eliasziw M et al. Extrauterine growth restriction and postnatal growth failure are misnomers for preterm infants. J Perinatol. 202025;40(5):704–14.
87. Kakatsaki I, Papanikolaou S, Roumeliotaki T, Anagnostatou NH, Lygerou I, Hatzidaki E. The prevalence of small for gestational age and Extrauterine Growth Restriction among extremely and very Preterm neonates, using different growth curves, and its association with clinical and nutritional factors. Nutrients. 2023;15(15):3290.
88. Clark RH, Wagner CL, Merritt RJ, Bloom BT, Neu J, Young TE, et al. Nutrition in the neonatal intensive care unit: how do we reduce the incidence of extrauterine growth restriction? J Perinatol. 2003;23(4):337–44.
89. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a Serious Problem in Prematurely Born neonates. Pediatrics. 2003;111(5):986–90.
90. Peila C, Spada E, Giuliani F, Maiocco G, Raia M, Cresi F et al. Extrauterine Growth Restriction: Definitions and Predictability of Outcomes in a Cohort of Very Low Birth Weight Infants or Preterm Neonates. Nutrients. 202026;12(5):1224.

Publisher's note