Clinical Endocrinology (2011) **75**, 335–341 doi: 10.1111/j.1365-2265.2011.04054.x

ORIGINAL ARTICLE

Postnatal growth and cardiometabolic profile in young adults born large for gestational age

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Summary

Context The association between large for gestational age (LGA) phenotype, postnatal growth and cardiometabolic risk (CMR) in adult life remains unclear. The role of *IGF1* genotype on LGA-related outcomes in adult life is unknown.

Aim To assess the postnatal growth, IGF-I levels, CMR and the influence of the *737.738 IGF1* in adults born LGA.

Subjects Case–control study (n = 515) nested in a population-based prospective cohort (n = 2063); 117 LGA and 398 gender-matched controls appropriate for gestational age (AGA) subjects.

Methods Anthropometry was evaluated at birth, at 9–10 and at 23–25 years old. At the age of 23–25 years, blood pressure (BP), glycaemia, insulinaemia, homeostasis model assessment – insulin resistance, lipids, fibrinogen, and plasma IGF-I and *737.738 IGF1* polymorphism were assessed.

Results Large for gestational age subjects remained heavier and taller than AGA at 9–10 and 23–25 years ($P < 0{\cdot}05$); at 23–25 years, LGA had greater waist circumference (WC; $P < 0{\cdot}05$) and higher BP ($P < 0{\cdot}05$) than controls. Body proportionality at birth did not predict metabolic outcome. LGA subjects presenting catch-down of weight in childhood had lower body mass index (BMI; $P = 0{\cdot}001$), lower WC ($P < 0{\cdot}05$) and lower BP ($P < 0{\cdot}05$) at 23–25 years. *737.738 IGF-I* genotype differed between groups ($P < 0{\cdot}001$). Homozygosis for polymorphic alleles was associated with increased odds of LGA (OR: 3·2; 95% CI: 1·5–6·9), higher IGF-I (56·9 ± 16·4 *vs* 37·7 ± 16·0 nM; $P < 0{\cdot}01$) and lower BP (114/68 *vs* 121/73 mmHg; $P < 0{\cdot}05$).

Conclusions Young adults born LGA presented higher BMI, WC and BP and appear to be at higher CMR risk than AGA subjects. The *737.738 IGF1* polymorphism appears to play a role on birth size and LGA-related metabolic outcomes.

(Received 24 November 2010; returned for revision 13 December 2010; finally revised 16 March 2011; accepted 16 March 2011)

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Introduction

Large for gestational age (LGA) infants are defined as having foetal or neonatal weight above the 90th percentile for an appropriate reference population for gestational age and sex.[1] Children born LGA remained taller and heavier at the age of 83 months. They are prone to excessive fat accumulation in early childhood, thereby increasing the risk for subsequent overweight.[1] The interest in the study of the LGA phenotype is growing because this condition has been associated with increased risk of obesity,[1] insulin resistance[2] and metabolic syndrome (MetS[3]) in later life.

The association of LGA phenotype, in the presence or absence of maternal gestational diabetes (GD), with the later onset of obesity and type 2 diabetes (T2D) was initially observed in Pima Indians.[4] In these subjects, this association was U shaped, with the highest prevalence of diabetes occurring in both high and low birth weight subjects.[4] Later, the relationship between LGA phenotype and development of MetS and T2D was also described in American children and adolescents.[3,5]

The mechanisms involved in being born LGA and its long-term consequences are less understood. Moreover, GD and maternal obesity, variations in genes related to the secretion and action of insulin, and insulin-like growth factors I (IGF-I) and II (IGF-II) may be implicated. IGF-I plays an essential role in growth and it has been implicated in the pathogenesis of T2D and cardiovascular disease.[6,7] The *737.738 IGF1* polymorphism is a microsatellite comprising a variable number of dinucleotide cytosine–adenine (CA) repeats in the promoter of the *IGF1* gene (OMIM* 147440, NM_000618.2). Studies have linked this polymorphism to variations in birth weight, IGF-I levels, increased risk for T2D and other cardiovascular risk factors. Most of these studies were cross-sectional and their results are conflicting.[8–11]

In the present study, we compared body proportionality at birth, pattern of postnatal growth, plasma IGF-I levels and metabolic parameters in early adult life in a large cohort of subjects born LGA with those of a control population born appropriate for gestational age (AGA). As no previous studies have focused on the possible association of the *IGF1* gene polymorphisms with LGA phenotype and its long-term consequences, we also evaluated whether variability in birth size and associated outcomes are related to the *737.738 IGF1* polymorphism.

Subjects and methods

Subjects

This was a case–control study nested in a population-based prospective cohort from Ribeirao Preto, Sao Paulo, Brazil. This cohort was evaluated in several phases. In the first phase (1978–1979), 9067 liveborns (98% of all births in the city) were examined and their mothers were interviewed. At 23–25 years of age (2001–2003), 2063 subjects were evaluated to analyse the influence of early events on chronic diseases in adult life. Final sample size calculation was described elsewhere.[12] Of these 2063 subjects, a subset of about 60% had been evaluated at 9–10 years to analyse childhood growth.

Anthropometry was performed at birth, at 9–10 and at 23–25 years. At 23–25 years, a fasting blood sample was collected for metabolic and hormonal measurements and DNA analysis. Technical procedures of anthropometric, clinical and biochemical measurements have been previously described.[12]

For the present study, among the 2063 subjects evaluated at 23–25 years, we investigated 93% of all LGA subjects in the entire cohort (n = 117) and a control group of AGA (n = 398) subjects. LGA and AGA groups were defined as birth weight for gestational age (BWGA) above the 90th percentile and from the 10th to the 90th percentile, respectively.[13] Nine of 126 (7%) LGA subjects were not included because of lack or low quality of blood samples to perform laboratory analyses. Gender-matched controls were randomly selected without replacement and represented 23% of all AGA subjects in the cohort. Selected and unselected AGA subjects did not differ regarding clinical parameters (data not shown). Subjects with endocrine disorders, chronic diseases, skeletal alterations, history of drug intake interfering with the somatotrophic axis, who were one of a twin pair or with incomplete data or gestational age lower than 37 weeks, were excluded.

All subjects gave written informed consent to participate, and the study was approved by the local ethics committee.

Phenotype outcomes

At birth. Weight and length standard deviation scores (SDS).[14] Roher's Ponderal Index (PI = weight × 100/length^3) was used to estimate body proportionality. PI above the 90th percentile or between the 10th and 90th percentiles indicated asymmetry or symmetry, respectively.[15]

At 9–10 years old. Weight, height and body mass index (BMI) SDS were evaluated in 55% of the LGA subjects (n = 64) and in 59% of the AGA subjects (n = 235). The differences between weight and height SDS at 9–10 years and weight and length SDS at birth ($\Delta_{0-9/10}$ SDS) of an individual described the growth pattern during this period. A decrease in SDS for weight >0·67 between birth and 9–10 years was considered to be a significant catch-down, as 0·67 SDS represents the width of each percentile band on standard growth charts, that is, 75th to 50th, 50th to 25th, 25th to 10th and so on.[16] For the purpose of this study, we only evaluated the influence of the catch-down of weight on cardiometabolic parameters in the beginning of adult life.

At 23–25 years old. Height SDS, BMI, waist circumference (WC, cm) and blood pressure (BP, mmHg). Procedures for BP estimation followed international standards and were reported in details previously.[12] Biochemical variables: fasting glucose, insulin, homeostasis model assessment – insulin resistance (HOMA-IR), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, IGF-I and fibrinogen levels. Plasma IGF-I levels were measured by RIA (DSL, Inc-5600); intra-assay and inter-assay variations were 3·0% and 10·8%, respectively.

Anthropometric SDS for sex and chronological age at 9–10 and 23–25 years were calculated using the references of the Center for Disease Control and Prevention.

Molecular analysis

Genomic DNA was isolated from peripheral blood leucocytes using a commercial kit (Qiagen, Hilden, Germany). The PCR was used to amplify the *737.738 IGF1* polymorphism, and the size of products was determined with an ABI 310 Analyzer, using ROX-500 as a fluorescent size marker.[17] The results were analysed using GENESCAN/GENOTYPER software (Applied Biosystems, Foster City, CA, USA). Results were confirmed by automatic sequencing in random samples (homozygous genotypes).

Statistical analysis

Hardy–Weinberg equilibrium was determined by the χ^2 test. Data are presented as mean ± SD. IGF-I levels were logarithm transformed because they had skewed distribution. In accordance with previous data,[18] subjects who were homozygous for the $(CA)_{19}$ or $(CA)_{20}$ alleles or were carriers of both the $(CA)_{19}$ allele and the $(CA)_{20}$ allele were considered to be homozygous wild type (WT). Carriers of two alleles that are both different from $(CA)_{19}$ and $(CA)_{20}$ were considered to be homozygous variant types (VT). Carriers of one WT allele and one VT allele were considered to be heterozygous. *737.738 IGF1* polymorphism was assessed according to co-dominant, dominant or recessive genetic model.

ANOVA was performed considering each phenotype outcome as the dependent variable and the interaction between *737.738 IGF1* genotype and BWGA status as the explanatory factor. The use of this interaction, instead of looking directly at the *IGF1* genotype alone, acknowledges the well-known influence of BWGA status on the dependent variables analysed. Analyses were adjusted for possible confounders at birth (gender, maternal smoking and educational level) and at the age of 23–25 years (gender, WC and height). Following ANOVA, orthogonal contrasts were estimated for pairwise group comparisons. The χ^2 test was performed to verify the association between genotype and BWGA status, and the odds ratio (OR) was calculated. A P value <0·05 was considered statistically significant. Sample size calculation of controls was based on an OR of 2 under the assumption of a 12% frequency of homozygous subjects for VT alleles[9] and a type 1 error probability of 5%. This gave a statistical power of 80%. All analyses were performed using the SAS software.

Results

Phenotype characteristics

The phenotypic characteristics of the two groups are shown in Table 1. There was no difference in gender between groups. At birth, there were more asymmetric subjects in the LGA than in the AGA group ($\chi^2 = 60{\cdot}6$; $P < 0{\cdot}001$). LGA subjects presented a higher risk for asymmetric foetal overgrowth than AGA subjects (OR: 6·5; 95% CI: 3·9–10·8).

At the age of 9–10 years, LGA subjects remained heavier and taller than AGA subjects. The growth pattern also differed between the two groups. Fifty of the 64 (78·1%) LGA subjects showed a significant catch-down, whereas this was observed in 68 of the 235 (28·9%) AGA subjects. At the age of 23–25 years, LGA subjects remained taller and heavier and had greater central adiposity and higher BP than AGA subjects. No differences in other cardiometabolic risk (CMR) factors were observed between groups at the age of 23–25 years.

We evaluated the influence of body proportionality at birth on anthropometry and other CMR factors at 23–25 years old. With the exception of a tendency to higher final height in symmetric LGA subjects (SDS: 0·82 ± 1·55 *vs* 0·25 ± 1·47; $P = 0{\cdot}05$), body proportionality at birth was not associated with CMR factors including BMI, WC, BP, lipids, glucose, insulin, HOMA-IR, fibrinogen and IGF-I levels (data not shown).

In addition, we also analysed the influence of the catch-down of weight between birth and 9–10 years old on CMR factors at 23–25 years of life. LGA subjects without catch-down showed higher BMI (29·4 ± 4·0 *vs* 24·9 ± 4·1 kg/m^2; $P = 0{\cdot}001$), WC (93·9 ± 10·7 *vs* 84·4 ± 13·1 cm; $P < 0{\cdot}05$) and diastolic BP (77 ± 7 *vs* 72 ± 11 mmHg; $P < 0{\cdot}05$) than LGA subjects with catch-down. These differences persisted after adjustment for WC, height and gender. No differences in other CMR factors were observed between groups. Compared with AGA subjects, even LGA subjects presenting catch-down had higher BMI (24·9 ± 4·1 *vs* 23·5 ± 4·4 kg/m^2; $P < 0{\cdot}05$) and WC (84·4 ± 13·1 *vs* 80·4 ± 11·9 cm; $P < 0{\cdot}05$). Catch-down of height in LGA subjects

Table 1. Phenotypic characteristics of LGA and AGA subjects

		BWGA		
Age		LGA	AGA	*P* value
Birth	*n* (male/female)	117 (56/61)	398 (178/220)	0·55
	Birth weight SDS	1·80 ± 0·53	−0·22 ± 0·72	<0·05
	Birth length SDS	0·66 ± 1·05	−0·64 ± 1·03	<0·05
	Gestational age	38·9 ± 1·7	38·9 ± 1·9	0·56
	PI < 90th percentile	72 (61·5%)	363 (91·2%)	<0·001
	PI ≥ 90th percentile	45 (38·5%)	35 (8·8%)	
9–10 years	*n* (male/female)	64 (28/36)	235 (105/130)	0·89
	Weight SDS	0·42 ± 0·90	−0·16 ± 1·21	<0·05
	Height SDS	0·35 ± 0·92	−0·09 ± 1·04	<0·05
	BMI SDS	0·37 ± 0·91	−0·12 ± 1·27	<0·05
	$\Delta_{0-9/10}$ weight SDS	−1·35 ± 1·00	0·13 ± 1·18	<0·05
	$\Delta_{0-9/10}$ height SDS	−0·45 ± 1·26	0·62 ± 1·53	<0·05
23–25 years	*n* (male/female)	117 (56/61)	398 (178/220)	0·55
	Adult height SDS	0·60 ± 1·54	−0·14 ± 1·48	<0·05
	BMI (Kg/m^2)*	25·6 ± 4·8	23·5 ± 4·4	<0·05
	WC (cm)†	85·3 ± 12·9	80·4 ± 11·9	<0·05
	SBP (mmHg)‡	120 ± 15	116 ± 15	<0·05
	DBP (mmHg)‡	72 ± 10	70 ± 8	<0·05
	IGF-I (nM)*	32·5 ± 16·9	32·2 ± 17·0	0·47
	Insulin (pM)‡	45·9 ± 42·3	44·7 ± 33·4	0·43
	Glucose (mM)‡	4·7 ± 0·5	4·7 ± 1·0	0·95
	HOMA-IR‡	1·4 ± 1·3	1·4 ± 1·2	0·38
	HDL cholesterol (mM)‡	1·2 ± 0·3	1·3 ± 0·3	0·18
	LDL cholesterol (mM)‡	2·8 ± 2·3	2·6 ± 1·4	0·27
	Triglycerides (mM)‡	0·7	1·0 ± 0·9	0·50
	Fibrinogen (μM)‡	9·0 ± 2·2	8·7 ± 1·9	0·58

Data are presented as means ± SD.
*Adjusted for gender.
†Adjusted for gender and height
‡Adjusted for gender, WC and height.
BWGA, birth weight for gestational age status; PI, ponderal index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AGA, appropriate for gestational age; HOMA-IR, homeostasis model assessment – insulin resistance; LGA, large for gestational age; SDS, standard deviation scores.

Table 2. Allele frequencies of *737.738 IGF1* polymorphism by phenotype groups

Allele (bp)	$(CA)_n$	LGA $n = 234$	AGA $n = 796$	All $n = 1030$
182	16	1 (0·004)	1 (0·001)	2 (0·002)
184	17	4 (0·02)	11 (0·01)	15 (0·01)
186	18	20 (0·08)	60 (0·07)	80 (0·08)
188	19 (WT)	115 (0·49)	419 (0·53)	534 (0·52)
190	20 (WT)	68 (0·29)	223 (0·28)	291 (0·28)
192	21	19 (0·08)	67 (0·08)	86 (0·08)
194	22	7 (0·03)	15 (0·02)	22 (0·02)

Data are presented in frequencies and proportions (between parentheses). AGA, appropriate for gestational age; CA, cytosine–adenine; LGA, large for gestational age; WT, wild type.

was not associated with cardiometabolic parameters in adult life (data not shown).

737.738 IGF1 polymorphism genotype

Genotype frequencies in the total number of subjects ($\chi^2 = 1{\cdot}18$; $P > 0{\cdot}05$) and in the LGA ($\chi^2 = 2{\cdot}22$; $P > 0{\cdot}05$) and AGA ($\chi^2 = 0{\cdot}08$; $P > 0{\cdot}05$) groups were in Hardy–Weinberg equilibrium. Seven alleles were observed according to the number of CA repeats (16–22). Table 2 shows the allele frequencies of the *737.738 IGF1* polymorphism found in LGA and AGA subjects. The most common alleles were $(CA)_{19}$ and $(CA)_{20}$.

737.738 IGF1 genotype vs BWGA Status

We compared the genotype frequencies between the two phenotype groups (Table 3). There were a significantly higher proportion of homozygous subjects for VT alleles among LGA than AGA subjects. Homozygosis for VT alleles appears to be associated with increased risk of being born LGA than AGA when they were compared with homozygosis for WT alleles or heterozygosis.

We also investigated the possible association between *737.738 IGF1* genotype and body proportionality at birth in LGA subjects. There were no differences in *737.738 IGF1* genotype distributions between symmetric and asymmetric overgrowth.

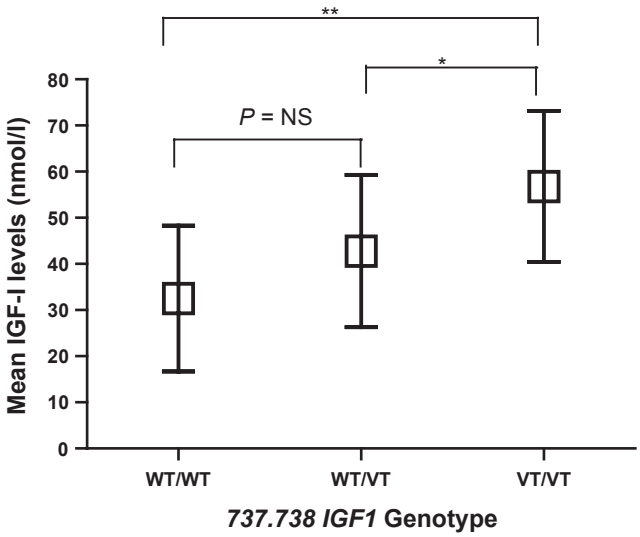

Fig. 1 Mean IGF-I levels in large for gestational age young adults according to the *737.738 IGF1* genotype. Data are expressed as mean ± SD. $^{**}P < 0.01$; $^{*}P < 0.05$. NS, not significant.

737.738 IGF1 genotype vs anthropometric outcomes at 9–10 years old

There was no association between *737.738 IGF1* genotype and the occurrence of catch-down in the LGA group.

Table 4 presents the influence of the *737.738 IGF1* polymorphism–BWGA status interaction on phenotype characteristics at the ages of 9–10 and 23–25 years in all subjects ($n = 515$). Table S1 (Supplemental Data) presents the phenotype characteristics according to the genotypes. At the age of 9–10 years, there was no influence of this polymorphism on weight, height, BMI, $\Delta_{0-9/10}$ weight or height SDS in LGA or AGA subjects (Table 4).

737.738 IGF1 genotype vs outcomes at 23–25 years old

In the LGA group, IGF-I levels were associated with *737.738 IGF1* genotype (Fig. 1). Homozygous subjects for VT alleles presented higher IGF-I levels than heterozygous subjects (56·9 ± 16·4 *vs* 42·7 ± 16·4 nM; $P < 0{\cdot}05$) and homozygous subjects for WT alleles (56·9 ± 16·4 *vs* 32·5 ± 15·7 nM; $P < 0{\cdot}01$). IGF-I levels were not

Table 3. Genotype frequencies of *737.738 IGF1* polymorphism by phenotype groups

	737.738 IGF1 genotype			
BWGA	WT/WT	WT/VT	VT/VT	
LGA ($n = 117$)	75 (64·1%)	29 (24·8%)	13 (11·1%)	$\chi^2 = 9{\cdot}5$
AGA ($n = 398$)	259 (65·0%)	124 (31·2%)	15 (3·8%)	$P = 0{\cdot}006$
Recessive model	VT/VT	WT/WT +WT/VT		
LGA ($n = 117$)	13 (11·1%)	104 (88·9%)		OR: 3·2
AGA ($n = 398$)	15 (3·8%)	383 (96·2%)		95% CI: 1·5–6·9

BWGA, birth weight for gestational age status; AGA, appropriate for gestational age; LGA, large for gestational age; VT, variant types; WT, wild type.

Table 4. The influence of the interaction between *737.738 IGF1* genotype and birth weight for gestational age status on phenotype characteristics in childhood and in early adult life (ANOVA)

Age (years)	Dependent variable	*P* value	R^2
9–10	Weight SDS	0·58	0·07
	Height SDS	0·84	0·09
	BMI SDS	0·71	0·04
	$\Delta_{0-9/10}$ weight SDS	0·82	0·29
	$\Delta_{0-9/10}$ height SDS	0·56	0·15
23–25	Height SDS	0·89	0·10
	Body mass index*	0·21	0·05
	Waist circumference†	0·24	0·19
	Systolic BP‡	**<0·05**	**0·41**
	Diastolic BP‡	**<0·05**	**0·29**
	IGF-I‡	**<0·05**	**0·55**
	Insulin‡	0·14	0·29
	Glucose‡	0·65	0·06
	HOMA-IR‡	0·14	0·22
	HDL cholesterol‡	0·36	0·09
	LDL cholesterol‡	0·64	0·06
	Triglycerides‡	0·96	0·12
	Fibrinogen‡	0·67	0·18

*Adjusted for gender.
†Adjusted for gender and height
‡Adjusted for gender, waist circumference and height.
Bold values indicate significant associations.
BMI, body mass index; HOMA-IR, homeostasis model assessment – insulin resistance; SDS, standard deviation scores.

different between homozygous subjects for WT alleles and heterozygous subjects (42·7 ± 16·4 *vs* 32·5 ± 15·7 nM; $P > 0·05$). In addition, homozygous subjects for VT alleles presented slight but significant lower BP than carriers of one WT allele (114/67 *vs* 120/73 mmHg; $P < 0·05$) or two WT alleles (114/67 *vs* 121/73 mmHg; $P < 0·05$). After adjustment for possible confounders, there was no influence of the *737.738 IGF1* genotype on adult height, BMI, WC or other metabolic parameters including fasting insulin and glucose, HOMA-IR, plasma lipids and plasma fibrinogen (Table 4).

Discussion

We showed that LGA subjects without catch-down during childhood presented higher BMI, central adiposity and diastolic BP than LGA subjects with catch-down at the age of 23–25 years. In the analysis of catch-down of weight, only half of LGA was included and we did not assess data of the first 2 years of life, where the greatest variation of weight occurs. However, these early changes in weight appear to persist throughout childhood.[16]

Previous data showed reduced insulin sensitivity in LGA newborns[2] and increased fat accumulation during childhood in LGA subjects.[1] However, one study demonstrated that obese children and adolescents born LGA without GD history exhibited lower central fat, higher peripheral fat and better insulin sensitivity profile.[19] To our knowledge, there were no data on anthropometric and metabolic outcomes in adults born LGA. Our findings showing that at the age of 23–25 years, independently of possible confounders, LGA subjects present higher BMI, central adiposity and BP than AGA controls and indicate that the unfavourable metabolic profile persists until adult life, as previously suggested in newborn and children LGA.[1–3] Although central adiposity has been estimated by WC, which is not the most accurate predictor of visceral fat, our results show the long-lasting consequences of the LGA phenotype, suggesting a higher risk to develop MetS.

Birth size results from the interaction of genetic and environmental factors. Information regarding maternal height, prepregnancy weight, pregnancy weight gain, history of GD and MetS in the family are lacking in the present study because these data were not collected in the original questionnaire applied in 1978–1979. However, our analyses were adjusted for other important confounders, including maternal educational level and smoking. It is noteworthy that previous studies have shown that history of GD has been observed in 20–27% of LGA newborns,[20,21] implying that most of the LGA offspring are born to nondiabetic mothers. Moreover, unfavourable metabolic profile at birth[20] and long-term LGA outcome are not exclusively related to maternal GD.[3,22,23]

We did not observe difference in plasma IGF-I between LGA and AGA adults, as observed in prepubertal LGA children.[24] Plasma IGF-I levels and birth size have been associated with *IGF1* polymorphisms, including the *737.738 IGF1* polymorphism.[8,10,25] In this Brazilian cohort, *737.738 IGF1* allele distribution was similar to that of previous studies in European populations.[10,11] We did not use the stratification of groups by ethnicity because in Brazilians, physical traits are poor predictors of genomic ancestry, estimated by molecular markers.[26,27]

We demonstrated association of the *737.738 IGF1* polymorphism with LGA phenotype. Homozygosis for VT alleles appears to triplicate the odds of being born LGA compared with AGA. As IGF-I levels at birth are positively associated with birth size,[28,29] this genotype may be associated with higher prenatal growth because of higher foetal IGF-I production. The influence of the *IGF1* genotype seems to persist throughout life, as demonstrated by lower IGF-I levels in LGA carriers of one or two copies of the WT alleles than in homozygous subjects for VT alleles.[30,31] The association between *737.738 IGF1* VT alleles and LGA phenotype is also in line with data showing higher BMI, fat mass and WC in children carrying these alleles.[20] The association of this polymorphism with birth weight is controversial. Three studies have reported higher birth weight in carriers of WT alleles,[8,10,32] whereas four studies could not confirm this association.[19,25,30,33] Most of these studies were cross-sectional, and birth weight was self-reported and analysed as a continuous variable.[8,10] In addition, only two previous studies divided the sample according to BWGA status into small for gestational age (SGA) and AGA and none of them showed significant differences in the allele distribution between these groups.[19,34] The present work is the first case–control study based on a prospective cohort with samples divided according to BWGA status into LGA and AGA subjects. Using these controlled parameters, we demonstrated that homozygosis for VT alleles triplicate the odds of being born LGA compared with AGA.

In our series, *737.738 IGF1*genotype was not associated with body proportionality at birth and did not influence postnatal anthropometry and the occurrence of catch-down of weight in LGA subjects. This suggests that *737.738 IGF1* genotype does not influence postnatal growth in LGA subjects, as observed in SGA subjects.[34]

Circulating IGF-I levels may be significant in the pathophysiology of cardiovascular diseases. IGF-I seems to be involved in the regulation of BP,[8] and low IGF-I levels seem to be associated with increased risk of T2D, endothelial dysfunction,[8] stroke and survival after stroke.[11] Higher IGF-I levels seem to reduce BP by increasing nitric oxide synthase bioactivity in the vascular endothelium, resulting in vasorelaxation.[8] However, to date, it is unclear whether changes in IGF-I levels are a cause or a consequence of these diseases.[11] Our data demonstrate an association among the *737.738 IGF1* polymorphism, variations in IGF-I levels and BP in young healthy adults, because LGA homozygous for VT alleles presented lower BP and higher IGF-I levels. These differences persisted after adjustment for possible confounders, including gender, WC and height, supporting a direct influence of this polymorphism on these variables. However, the influence of additional potential confounders such as smoking, physical activity or dietary consumption was not analysed. The differences between LGA homozygous for VT and LGA carriers of WT alleles regarding BP and IGF-I levels are small and their clinical relevance remains to be established. Epidemiological studies had shown that reduction as small as 5 mmHg in diastolic BP decreases the risk of stroke and coronary disease. In addition, the studied subjects are healthy and young and it is possible that these differences will become more relevant in later life.

Regarding the association between *737.738 IGF-I* polymorphism and plasma IGF-I, our results demonstrated the association between VT alleles and higher plasma IGF-I, which is in agreement with two studies conducted on the general population,[30,31] while another group demonstrated the opposite.[8] These conflicting results may reflect differences in data acquisition and analysis. It is possible that the ethnical composition of the analysed samples lies behind this controversy because ethnicity seems to influence circulating IGF-I levels and its binding proteins, as demonstrated in one study in White and African-American pubertal subjects.[35]

Conclusions

In the beginning of adult life, subjects born LGA, especially those who did not experience catch-down of weight during childhood, appear to present a less-favourable cardiometabolic phenotype represented by higher BMI, central adiposity and higher BP. Homozygosis for *737.738 IGF1* VT alleles was associated with higher plasma IGF-I and lower BP in young adult LGA subjects. Whether this genotype represents a protective trait for cardiovascular disease in subjects born LGA remains to be established. Further studies analyzing the interaction of this genotype with LGA-related outcomes in different cohorts are needed. In addition, re-evaluation of this cohort in the next decades will be also important to assess the clinical relevance of the present findings on CMR.

Acknowledgements

This work was supported by grants 06/50570-4 and 07/58105-1 from 'Fundacao de Amparo a Pesquisa do Estado de Sao Paulo' (FAPESP), Brazil. We acknowledge all the participants of the cohort studied for their contribution to making this study possible.

Conflict of interest

The authors declare that they have no competing financial interests.

Financial disclosure

There are no financial relationships relevant to this article to disclose.

Author's contribution

A.R.E. and S.R.A. planned the study, analysed data and wrote the manuscript with inputs from M.C. and F.L.F-R.. A.R.E and A.C.B. performed DNA sampling and genotype analysis. R.M.S and A.R.E. performed statistical analysis. A.C.M. contributed to the IGF-I measurements and analysis. M.A.B and H.B. conducted the longitudinal cohort study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Phenotype characteristics of LGA and AGA subjects after stratification for *737/738 IGF-I* polymorphism genotype (ANOVA) at infancy and at early adult life.

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