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Undernutrition and suboptimal growth during the first year are associated with glycemia but not with insulin resistance in adulthood

Desnutrición y crecimiento insuficiente durante el primer año están asociados con la glucemia, pero no con la resistencia a la insulina en la etapa adulta

Subnutrição e crescimento baixo durante o primeiro ano de vida estão associados à glicemia, mas não à resistência insulínica na vida adulta

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Abstract

This study aimed to assess whether weight, length, and conditional growth during the first year are associated with glycemia and insulin resistance among young adults. A non-concurrent longitudinal design was used in the study. This is a population-based cohort study, composed of people aged from 22 to 28 years. We estimated z-scores from birth to the first year and the infants were classified as stunted, underweight, overweight, obese, wasted, and at risk of wasting, using cut-offs proposed by the World Health Organization (Child Growth Standards, 2006)*. Conditional weight and length gain variables were estimated. Glycemia, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and single point insulin sensitivity estimator (SPISE) were evaluated in adulthood. Multiple linear regressions that includes the variables associated with glycemia and insulin resistance were used. In total, 1,070 subjects were evaluated and glycemia in adulthood was higher among subjects who were wasted or at risk of wasting at 12 months (β coefficient = 2.77; 95%CI: 0.37; 5.21). In relation to normal weight, those subjects who were overweight at 12 months showed the lowest glycemia (β coefficient = -2.39; 95%CI: -4.32; -0.36). Conditional weight gain in the first year was negatively associated with glycemia in adulthood (β coefficient = -0.65; 95%CI: -1.23; -0.08). SPISE was higher among underweight subjects, and negatively associated with conditional relative weight gain and conditional linear growth in the first year. In conclusion, we found that undernutrition and suboptimal growth were associated with higher glycemia.*

Type 2 Diabetes Mellitus; Insulin Resistance; Young Adult; Growth

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Introduction

The prevalence of noncommunicable diseases (NCDs), such as type 2 diabetes mellitus, reached epidemic proportions worldwide. In the natural history of this disease, there are three developmental stages: compensatory hyperinsulinemia, prediabetes, and diabetes. In the first, the insulin resistance is present, but the β-cell mass retains the ability to synthesize insulin in adequate amounts for metabolic requirements. In the second stage, fasting glycemia values can be higher than 100mg/dL, but never exceeds 126mg/dL. And in the third stage, there are manifest disorders of carbohydrate metabolism, and fasting glycemia at any time of the day is higher than 126mg/dL [1,2,3,4,5].

The recognition of insulin resistance in persons at risk is significant to implement preventive measures, since type 2 diabetes mellitus causes major health care costs and burden for the patient. The standard technique for assessment of insulin sensitivity is the hyperinsulinemic-euglycemic clamp, however, although this technology has been used to study the insulin secretion and the insulin sensitivity, it is time-consuming and difficult to apply method in epidemiological studies. The homeostasis model assessment of insulin resistance (HOMA-IR) approach, introduced by Matthews et al. has been widely used in clinical research to assess insulin sensitivity [6], however, it is not clear which cut-off value is the best to define insulin resistance and it has been described significant differences in insulin levels in different countries [7]. Moreover, single point insulin sensitivity estimator (SPISE) is another formula to calculate IR and smaller scores are associated with insulin resistance [8].

Concerning the life cycle determinants of type 2 diabetes mellitus, it has been reported that birth weight, breastfeeding, nutritional status, and early growth would be associated with later risk of type 2 diabetes mellitus [9,10,11,12,13,14]. The faster growth in childhood would yield adjustment of hepatic metabolism, that regulates the production of endogenous glucose, mostly through glycogenolysis and gluconeogenesis [3,5]. On the other hand, it was also reported that poor nutrition in early childhood results in a high risk of chronic diseases associated with an alteration of body composition [15,16,17,18,19].

Low birth weight subjects that also presented undernutrition in postnatal life have higher mortality by cardiovascular disease in adulthood [18]. Indeed, in the *Helsinki Birth Cohort Study*, and Hertfordshire cohort, type 2 diabetes mellitus was associated with low weight in the first year [20,21]. Being born small for gestational age, or being stunted at age 2 years were both inversely associated with lean mass in adulthood, possible explanations are related to the preferential restriction of skeletal muscle growth that occurs during growth restriction [19]. It seems clear that undernutrition in critical periods affects the development of pancreatic β-cells, which would lead to β-cell failure and the development of type 2 diabetes mellitus [22].

Conditional variables express how a child deviates from its expected height or weight, based on its previous measures and the growth of the studied population [23]. Evidence about the long-term consequences of weight gain in childhood is not as clear [24]. It has been reported that excessive weight gain in every age range from birth to mid-childhood increases the risk of NCDs [25], on the other hand, it has been reported that this association may be modified by the timing of weight gain [26]. A study in low- and middle- income countries observed an association of conditional relative weight gain at 2 years old with the risk of adult overweight and a slightly increase in the risk of elevated blood pressure, but it was unrelated to dysglycemia [27]. However, faster mid-childhood relative weight gain was strongly associated with fat mass than fat-free mass, and increased the risk of elevated blood pressure and dysglycemia [27].

Adair et al. [27] observed that faster linear growth at 2 years was associated with a reduced risk of high fat-free mass (β coefficient [β] = 0.40), (95% confidence interval [95%CI]: 0.37; 0.42) than a reduced risk of high fat mass (β = 0.27; 95%CI: 0.25; 0.29), and increased the likelihood of adult overweight (β = 1.24; 95%CI: 1.17; 1.31) (mostly related to lean mass). Although, in the Birth to Twenty Plus cohort, relative linear growth at all-time points except for between years 5-8 was associated with increased fat mass at 22 years [28].

In light of the evidence, it is important to assess age-specific conditional measures, considering the strong correlation between repeated measurements over time and avoiding the "reversal paradox" [29]. Our research group thought that suboptimal growth at age 0-1 year tend to determine higher risk of dysglycemia and insulin resistance among young adults. Such diseases need to be studied based on a life-course perspective, and prenatal and childhood growth need to be considered in order to

understand the pathogenesis of several NCDs, as indicated by Eriksson [30]. This study used data from the cohort of newborns in Limache and Olmué in Chile in the years 1974-1978 and 1988-1992 (1,070 participants, aged between 22 and 28 years), and aimed to investigate whether weight, length, and conditional growth during the first year are associated with glycemia and insulin resistance that are determinants of type 2 diabetes mellitus among young adults.

Materials and methods

Study design

A non-concurrent longitudinal design was used in the study, which was located in the region of Valparaiso, Chile, in the municipalities of Limache and Olmué. These municipalities are relatively near to the country's capital city of Santiago. Currently, the total population of both municipalities combined is 63,637 inhabitants and the Human Development Index (HDI) is 0.726 in Limache and 0.712 in Olmué (Instituto Nacional de Estadísticas Chile. Censos de población y vivienda 2002 y 2017. https://reportescomunales.bcn.cl/2017/index.php/Limache/Población, accessed on 16/Jun/2019) (Programa de las Naciones Unidas para el Desarrollo. http://desarrollohumano.cl/idh/category/serie-dh-s/, accessed on 13/Jun/2019), though, at the time this study started, in 2001, the numbers were similar, 0.722 and 0.701 respectively [31]. The participants were sons and daughters of women residing in these municipalities. Data from two cohorts of people born in 1974-1978 (Cohort 1) and 1988-1992 (Cohort 2) were evaluated.

The survey in Cohort 1 involved 1,232 participants randomly selected from 3,096 children born between 1974 and 1978. The Cohort 2 included 1,000 participants randomly selected from 2,650 children born between 1988 and 1992. Exclusion of people with missing data for birth weight, fasting plasma glucose (FPG), and fasting insulin resulted in an analytical sample of 1,941 study participants. The Cohort 1 was initially evaluated between 2001 and 2003 when the participants were aged from 22 to 28 years. The subjects were interviewed about socioeconomic and behavioral variables, they were examined (anthropometry, blood pressure) and donated a blood sample. Furthermore, trained personnel collected data from the birth records, pediatric clinical notes which provided data on birth anthropometry and the first year of life, and diseases diagnosed in the primary care center. The data collection in Cohort 2 was carried out from 2015 to 2018 and followed the same procedures. Further details on the study methodology have been published elsewhere [32,33].

Information on birthweight, gestational age, and weight and length in the first year were collected from health records. The birth records at Chilean health services contain data about the mothers as well as their newborn babies. Length in the first year was recorded to the nearest 0.5cm and weight to the nearest 0.5kg. Birth weight was recorded for 1,941 babies, and anthropometric measurements in the first year for 1,070, on which most of our analyses are based.

Socioeconomic information, behavioral measures, feeding practices, and physical activity were evaluated using a structured questionnaire applied by interviewers when the participants were aged between 22 and 28 years. In adulthood, anthropometric measures were assessed, by trained nutritionists. Subjects were weighed and measured with light clothing, according to standardized techniques. Blood sample was obtained following a 12-h fast. HDL cholesterol was measured by precipitation according to the technique of Seigler and Wu and triglycerides were measured using enzymatic methods (HUMAN factor, Gesellschaft für Biochemica und Diagnostica, Germany). An enzymatic colorimetric method (GOD/PAP, Human Diagnostic, Germany) was used to record blood glucose levels. Additionally, insulin was determined by radioimmunoassay to calculate insulin resistance using the HOMA-IR.

Outcomes

Glycemia (mg/dL), fasting insulin (μU/mL), HOMA-IR, and SPISE were evaluated in adulthood, at a mean age of 24.7 years.

The following formulas were used for HOMA-IR and SPISE:

$$\text{HOMA-IR: glycemia x insulin}/405$$

$$\text{SPISE: } 600 \times HDL^{0.185}/(TG^{0.2} \times BMI^{1.338})$$

Insulin resistance was defined by an HOMA-IR score higher than 2.6 and SPISE lower than 6.61 [8,31]. HOMA and SPISE were analyzed as continuous outcome too.

Nutritional status

Using the *WHO Child Growth Standards, 2006* [34], we estimated length-for-age (LAZ), weight-for-length (WLZ), weight-for-age and birthweight (WAZ) z-scores. WHO Anthro version 3.2.2 (https://www.who.int/tools/child-growth-standards/software) was used in processing anthropometric data; 0.25% of measurements were excluded from the analyses, after being flagged as outliers according to the valid ranges accepted by WHO (WAZ < -6 or > 5; LAZ < -6 or > 6; WLZ < -5 or > 5 z-scores).

Infants with a LAZ 2 standard deviation (SD) or more below the World Health Organization (WHO) reference were classified as stunted and < -3 SD as severely stunted. Infants with a WAZ 2 SD or more below the WHO reference were classified as underweight, and severe underweight as a z score < -3 SD. Those with WLZ > 2 SD above WHO reference were classified as overweight and > 3 SD as obese. A child whose WLZ was less than -2 SD was deemed wasted and at risk of wasting with a WLZ < -1 SD [35,36].

Conditional growth

Conditional variables were obtained by regressing weight or length on birthweight and earlier measures of weight and length, and standardized residuals were derived. At each time point, the conditional variable represents growth during a time interval, and a positive value represents a weight gain or linear growth faster than predicted in that period. To estimate the conditional, length at a given age, length was regressed on previous weight and length. Therefore, conditional length at 12 months of age was estimated by regressing LAZ z-scores in this same period on birthweight. On the other hand, conditional relative weight gain was estimated from length at that age and previous measures of length and weight. Therefore, conditional relative weight was derived by regressing weight and length at 12 months of age on birthweight.

Confounding variables

Socioeconomic level was defined on schooling and occupation of the main home breadwinner, generating 6 socioeconomic groups. This classification was based on social stratification matrix method proposed by the European Society for Opinion and Marketing Research (ESOMAR), validated in Chile [37]. In this study, due to the lack of people in the two upper categories, we established four categories: (i) very low; (ii) low; (iii) middle and (iv) high.

Information on birthweight in grams and gestational age in weeks were retrieved from health records. Birth cohort was defined as based on the year of birth.

Data analyses

Descriptive analyses included calculation of means and standard deviations for quantitative variables and proportions and 95%CI for categorical outcomes.

Multiple linear regression was used to adjust the estimates for the following confounders: sex, socioeconomic level, birthweight, and gestational age. We tested whether birth cohort had an association with nutritional status and conditional growth during the first year and at the same time with adult glycemia and insulin resistance. The associations with conditional length, LAZ, and WAZ were

significant (p = 0.045, 0.004, and 0.012 respectively). Preliminary analysis showed that the additional associations tested, including WLZ, conditional relative weight, Glycemia, fasting insulin, HOMA-IR, and SPISE were not significant (data not shown). Therefore, we considered birth cohort as a confounder variable in the adjusted analyses.

Furthermore, for conditional length gain from birth to 6 months of age, estimates were also adjusted for birthweight z-score and length at birth z-score. On the other hand, both conditional relative weight gain and conditional length gain were controlled from birth to 6 months of age. For conditional length gain from 6 to 12 months of age, estimates were also adjusted for LAZ and WAZ at 6 months, length at birth and birthweight z-score and for relative weight gain also from 6 to 12 months of age.

Statistical significance level was defined by a p-value (α) of < 0.05. Data analysis was performed using Stata version 13.0 (https://www.stata.com/).

Ethical aspects

Young adults were invited to participate in the study and asked to sign the informed consent form prior to data collection. The study protocol was approved by the Ethics Research Committee of Faculty of Medicine of University of Chile and carried out by the Department of Nutrition, with the support of Wellcome Trust and the National Research Fund of Chile (Fondecyt). All surveys used a similar methodology [33].

Results

In the original cohorts, 2,232 subjects were interviewed. Information on blood sample at 22-28 years of age was available for 1,941 subjects (87% of the original sample). We were able to get information on weight and length from birth to 12 months from 1,070 individuals (47.9% of the original cohort). Supplementary Material (http://cadernos.ensp.fiocruz.br/static//arquivo/suppl-e00120320_4316.pdf) shows that those subjects who were included in the current analysis were similar to those who were excluded, according to anthropometry at birth, anthropometric measurements in adulthood, and biochemical parameters.

The mean age at the time of assessment in adulthood was 24.7 years. Table 1 shows characteristics of the studied subjects according to sex. For males, mean birth weight was 3,230g, whereas for women was 3,170g (p < 0.0001), mean length at birth was 49.6cm and 49.3cm for men and women (p < 0.0001), respectively. Prevalence of insulin resistance according to HOMA-IR was 36.6% (95%CI: 34.4; 38.9) and SPISE was 54.8% (95%CI: 51.8; 57.9). Mean SPISE was 6.46 (SD = 1.83), fasting glycemia 85.7mg/dL (SD = 9.50), and fasting insulin 11.49μU/mL (SD = 4.65), with differences between men and women (p < 0.0001). Prevalence of prediabetes (glycemia fasting level ≥ 100mg/dL and < 126mg/dL) was 4.5% and 0.3% of diabetes (glycemia fasting level ≥ 126mg/dL), higher in males (p = 0.008).

Table 2 shows that those subjects who were stunted at 12 months were more likely to have higher glycemia, but this relation was no longer statistically significant (p = 0.11) after the adjustment for sex, cohort of birth, gestational age, birthweight and socioeconomic level. SPISE was higher among underweight subjects (β = 0.82; 95%CI: 0.27; 1.37), wasting and at risk of wasting was positively associated with glycemia (β = 2.67; 95%CI: 0.19; 5.14). Independent of birth weight and the other covariates (sex, socio-economic level, cohort, and gestational age), higher WLZ at 12 months was associated with lower glycemia (β = -2.39; 95%CI: -4.32; -0.36).

Table 3 shows that conditional relative weight gain in the first year was negatively associated with glycemia in adulthood (β = -0.65; 95%CI: -1.23; -0.08), and this was mainly due to weight gain in the first months of life. For instance, higher weight accretion from 0 to 6 months was associated with a lower glycemia (β = -0.83; 95%CI: -1.44; -0.22), meanwhile from 6 to 12 months weight accretion was not statistically associated with glycemia (β = -0.07; 95%CI: -0.68; 0.55). Negative associations were also observed for conditional relative weight gain at 6 and 12 months of life with SPISE. Conditional linear growth at 6 months was negatively related to SPISE. There was no association of relative condi-

Table 1

Characteristics of the study subjects.

	Male (n = 468)	Female (n = 602)	All (n = 1,070)
Born			
Birth weight (g) *	3,230 ± 560	3,170 ± 510	3,190 ± 540
Length at birth (cm) *	49.60 ± 2.00	49.30 ± 2.10	49.48 ± 2.12
First year			
Conditional relative weight gain 12 months (z-score) **	-0.00 ± 1.10	0.00 ± 1.00	0.04 ± 0.97
Conditional linear growth 12 months (z-score) *,***	-0.20 ± 1.10	0.10 ± 0.90	-0.01 ± 0.95
First semester of life			
Conditional relative weight gain 6 months (z-score) #	-0.11 ± 1.04	0.08 ± 0.97	-0.00 ± 1.00
Conditional linear growth 6 months (z-score) ##	-0.21 ± 1.08	0.16 ± 0.90	-0.00 ± 1.00
Second semester of life			
Conditional relative weight gain 6 to 12 months (z-score) ###	0.08 ± 1.08	-0.06 ± 0.93	0.00 ± 1.00
Conditional linear growth 6 to 12 months (z-score) §	-0.05 ± 1.08	0.04 ± 0.93	-0.00 ± 1.00
Adulthood			
Age (years) *	24.82 ± 1.49	24.55 ± 1.58	24.67 ± 1.55
BMI *	25.79 ± 4.14	26.44 ± 5.17	26.11 ± 4.73
Glycemia (mg/dL) *	87.7 ± 10.4	84.4 ± 8.9	85.70 ± 9.50
Fasting Insulin (μU/mL) *	11.3 ± 4.7	11.7 ± 4.6	11.49 ± 4.65
HOMA-IR *,§§	2.48 ± 1.20	2.47 ± 1.10	2.47 ± 1.13
SPISE *,§§§	6.40 ± 1.70	6.50 ± 1.90	6.46 ± 1.83
Percent located at 22-28 years of age			
Insulin resistance (HOMA-IR)	33.62	34.77	34.27
Insulin resistance (SPISE)	56.71	53.39	54.83
Prediabetes (fasting plasma glycemia: 100-125mg/dL) *	6.47	2.97	4.49
Diabetes (fasting plasma glycemia ≥ 126mg/dL) *	0.43	0.17	0.28

BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; SIPSE: single point insulin sensitivity estimator.

* Differences significant at the 0.05 level;

** Conditional relative weight gain was predicted with weight-for-age z-scores (WAZ) at 11 and 12 months modelled using length-for-age z-scores (LAZ) at 11 and 12 months, LAZ at birth and WAZ at birth;

*** Conditional linear growth was predicted with LAZ at 11 and 12 months modelled using LAZ at birth and WAZ at birth;

Conditional relative weight gain was predicted with WAZ at 4, 5, 6 and 7 months modelled using LAZ at 4, 5, 6 months and 7, LAZ at birth and WAZ at birth;

Conditional linear growth was predicted with LAZ at 4, 5, 6 and 7 months modelled using LAZ at birth and WAZ at birth;

Conditional relative weight gain was predicted with WAZ at 11, 12 months modelled using LAZ at 11, 12 months, LAZ at 4, 5, 6 and 7 months and WAZ at 4, 5, 6 and 7 months;

§ Conditional linear growth was predicted with LAZ at 11, 12 months modelled using LAZ at 4, 5, 6 and 7 months and WAZ at 4, 5, 6 and 7 months;

§§ Glycaemia * fasting insulin/405;

§§§ $600 \times HDL^{0.185}/(TG^{0.2} \times BMI^{1,338})$.

tional weight gain and conditional linear growth during the first year with other results related to the metabolism of carbohydrate and IR, such as the level of fasting insulin, HOMA-IR index, prediabetes, and diabetes.

Table 2

Coefficients from multiple linear regression relating glucidic metabolism and insulin resistance in young adults according to nutritional status at 12 months (n = 1,070).

	Glycaemia (mg/dL) β (95%CI)		Fasting insulin (μU/mL) β (95%CI)		HOMA-IR β (95%CI)		SPISE β (95%CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Length-for-age z-scores	p = 0.03	p = 0.11	p = 0.36	p = 0.82	p = 0.24	p = 0.62	p = 0.05	p = 0.09
Stunting	1.74	1.20	-0.12	-0.08	0.04	0.04	0.27	0.21
	(0.17; 3.33)	(-0.34; 2.75)	(-0.88; 0.64)	(-0.83; 0.65)	(-0.14; 0.23)	(-0.14; 0.22)	(-0.02; 0.57)	(-0.08; 0.50)
At risk of stunting	-0.40	-0.55	-0.32	-0.36	-0.09	-0.11	0.25	0.23
	(-1.73; 0.93)	(-1.93; 0.83)	(-0.96; 0.33)	(-1.02; 0.30)	(-0.25; 0.06)	(-0.27; 0.05)	(0.00; 0.50)	(-0.03; 0.49)
Normal length (reference)	-	-	-	-	-	-	-	-
Weight-for-age z-scores	p = 0.04	p = 0.57	p = 0.33	p = 0.17	p = 0.12	p = 0.28	p = 0.00	p = 0.00
Underweight	0.48	0.83	-0.64	-0.83	-0.09	-0.18	0.81	0.82
	(-2.37; 3.32)	(-3.73; 2.07)	(-2.01; 0.73)	(-2.23; 0.56)	(-0.42; 0.24)	(-0.52; 0.15)	(0.28; 1.35)	(0.27; 1.37)
At risk of underweight	1.84	1.27	0.37	0.08	0.16	0.09	0.36	0.42
	(0.09; 3.38)	(-0.50; 3.04)	(-0.47; 1.21)	(-0.77; 0.94)	(-0.04; 0.36)	(-0.11; 0.30)	(0.03; 0.70)	(0.08; 0.75)
Eutrophic (reference)	-	-	-	-	-	-	-	-
Weight-for-length z-scores	p = 0.02	p = 0.02	p = 0.50	p = 0.28	p = 0.23	p = 0.33	p = 0.43	p = 0.24
Wasting and at risk	2.77	2.67	0.93	-0.03	0.18	0.08	0.17	0.27
	(0.37; 5.21)	(0.19; 5.14)	(-0.77; 1.53)	(-1.22; 1.16)	(-0.10; 0.47)	(-0.20; 0.37)	(-0.27; 0.64)	(-0.20; 0.73)
Overweight and obesity	-2.20	-2.39	-0.31	-0.16	-0.11	-0.10	-0.03	-0.08
	(-4.14; -0.26)	(-4.32; -0.36)	(-1.24; 0.63)	(-1.10; 0.78)	(-0.34; 0.12)	(-0.33; 0.12)	(-0.40; 0.33)	(-0.44; 0.30)
Normal weight (reference)	-	-	-	-	-	-	-	-

95%CI: 95% confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance; SPISE: single point insulin sensitivity estimator.
Note: models were adjusted for sex, family income, cohort, gestational age and birthweight.

Discussion

Wasting individuals and at risk of wasting at their first year was positively associated with glycemia, on the other hand, overweight and obesity was only negatively associated with glycemia. Independent of birth weight, relative weight gain from 0 to 12 months was negatively associated with glycemia and SPISE.

We studied more than 1,000 adults who were born at a time of rapid nutritional transition. This study confirms the low prevalence of impaired fasting glucose (IFG) and type 2 diabetes mellitus among young adults. On the other hand, the prevalence of insulin resistance was 36.6% and mean HOMA-IR was 2.5. The study highlighted the high prevalence of insulin resistance measured by SPISE. This suggests that the components of each index influence the insulin resistance prediction. We believe that SPISE has partial low values because of blood lipids profile and body mass index (BMI) effects, consistent with prior analysis in these cohort [32,38]. If more studies were replicated with these two indices, it would greatly increase our knowledge about the best mechanism to diagnose insulin resistance in the population. Also, it would provide further knowledge for directing interventions to prevent type 2 diabetes mellitus, with an emphasis on those who are in the first stage of the disease.

This study results demonstrated that early life adversity has a consistent and significant effect on later development of risk factors associated with type 2 diabetes mellitus. Individuals stunted in the first year showed higher glycemia, but after controlling for confounders, the magnitude of the association decreased and the confidence interval slightly included the reference. Therefore, we cannot discard that this association was due to the random. Our findings are remarkably similar to those of Reid et al. [39], who observed that stunted individuals at early years have higher risk of metabolic disorders in adolescence (total cholesterol, low-density lipoprotein cholesterol, triglycerides, insulin, and HOMA-IR).

Table 3

Coefficients from multiple linear regression, relating glucidic metabolism and insulin resistance in young adults according to conditional linear growth and conditional relative weight gain (z-score) during first year of life (n = 1,070).

	Glycaemia (mg/dL) β (95%CI)		Fasting insulin (μU/mL) β (95%CI)		HOMA-IR β (95%CI)		SPISE β (95%CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Birth to 12 months								
Conditional relative weight gain (n = 1,070) *	-0.73 (-1.31; -0.15)	-0.65 (-1.23; -0.08)	0.03 (-0.36; 0.44)	-0.01 (-0.29; 0.26)	-0.03 (-1.23; 0.08)	-0.01 (-0.12; 0.09)	-0.17 (-0.27; -0.06)	-0.19 (-0.30; -0.08)
Conditional linear growth (n = 1,070) **	-0.26 (-0.84; 0.32)	-0.07 (-0.52;- 0.66)	0.21 (-0.19; 0.61)	0.23 (-0.05; 0.52)	0.00 (-0.10; 0.11)	0.00 (-0.09; 0.11)	-0.12 (-0.23; -0.09)	-0.14 (-0.26; -0.03)
Birth to 6 months								
Conditional relative weight gain (n = 925) ***	-0.80 (-1.41; -0.20)	-0.83 (-1.44; -0.22)	0.03 (-0.27; 0.33)	0.07 (-0.22; 0.37)	-0.02 (-0.09; 0.05)	-0.01 (-0.08; 0.06)	-0.15 (-0.27; -0.03)	-0.17 (-0.29; -0.05)
Conditional linear growth (n = 925) #	-0.20 (-0.81; 0.41)	-0.21 (-0.83; 0.40)	0.14 (-0.16; 0.44)	0.19 (-0.11; 0.49)	0.01 (-0.06; 0.09)	0.02 (-0.48; 0.10)	-0.10 (-0.22; 0.01)	-0.11 (-0.23; 0.01)
6-12 months								
Conditional relative weight gain (n = 925) ##	-0.12 (-0.73; 0.49)	-0.07 (-0.68; 0.55)	-0.03 (-0.33; 0.27)	0.03 (-0.26; 0.33)	-0.01 (-0.08; 0.06)	0.01 (-0,07; 0.08)	-0.15 (-0.22; 0.02)	-0.12 (-0.23; 0.00)
Conditional linear growth (n = 925) ###	-0.20 (-0.81; 0.41)	-0.17 (-0.78; 0.44)	0.18 (-0.12; 0.43)	0.19 (-0.11; 0.49)	0.03 (-0.04; 0.10)	0.03 (-0.04; 0.11)	-0.02 (-0.14; 0.10)	-0.02 (-0.14; 0.10)

95%CI: 95% confidence interval; HOMA-IR: homeostasis model assessment of insulin resistance; SPISE: single point insulin sensitivity estimator.
Note: models were adjusted for sex, family income, cohort, gestational age and birthweight.
* Conditional relative weight gain was predicted with weight-for-age z-score (WAZ) at 11 and 12 months modelled using length-for-age z-score (LAZ) at same period, LAZ at birth and WAZ at birth;
** Conditional linear growth was predicted with LAZ at 11 and 12 months modelled using LAZ at birth and WAZ at birth;
*** Conditional relative weight gain was predicted with WAZ at 4, 5, 6 and 7 months modelled using LAZ at 4, 5, 6 months and 7, LAZ at birth and WAZ at birth;
# Conditional linear growth was predicted with LAZ at 4, 5, 6 and 7 months modelled using LAZ at birth and WAZ at birth;
Conditional relative weight gain was predicted with WAZ at 11, 12 months modelled using LAZ at 11, 12 months, LAZ at 4, 5, 6 and 7 months and WAZ at 4, 5, 6 and 7 months;
Conditional linear growth was predicted with LAZ at 11, 12 months modelled using LAZ at 4, 5, 6 and 7 months and WAZ at 4, 5, 6 and 7 months.

Young individuals exposed to wasting and at risk of wasting at one year, demonstrated higher glycemia. Notably, this association was independent of birth weight, sex, gestational age, and current socioeconomic level. These results suggest that early life malnutrition may increase the risk of carbohydrate metabolism-related disorders.

On other hand, underweight at first year of life was associated with higher mean of SPISE levels, regardless of sex, socioeconomic level, birth cohort, gestational age, and birthweight. Other studies suggested that individuals who are small in the first years of life, present greater risk for several metabolic conditions as impaired glucose tolerance [40,41]. This aspect highlights the need for more studies focusing on SPISE and other tests for insulin resistance which are based on lipoprotein metabolism and nutritional status. For example, SPISE was applied only in studies of European countries, and it may be inappropriate for other populations [8]. We cannot rule out the possibility of unfitness of SPISE to evaluate insulin resistance in this population.

Overweight children at one year presented lower glycemia in the adulthood, but they did not present lower insulin, HOMA-IR nor higher SPISE. Previous studies on the association of overweight at childhood with glycemia, insulin, and insulin resistance have shown mixed results [1,42,43]. There have been few studies of adults with a history of overweight at first year that report disorders of carbohydrate metabolism, and the results of these studies have shown either the same relationship or no relationship, when compared with our study [40,44].

In this cohort study, changes in WAZ were strongly associated with glycemia at the age of 22-28 years, suggesting that the risk for high glycemia may be associated with poor relative weight gain in the first year. Furthermore, this study showed that weight gain during the first, but not the second 6 months of life was related with lower glycemia, a condition usually associated with lower risk of type 2 diabetes mellitus.

Notably, we were unable to find in the published literature the association of weight gain in the first 6 months of life or between 0 and 12 months with lower SPISE at adult age. Suggesting that early childhood relative weight gain is associated with increased insulin resistance measured by SPISE. Based on these contradictory results, it is unlikely that relative weight gain fully explains the association, which, in fact, SPISE values are influenced by currently nutritional status and blood lipids. One may speculate that the rapid weight gain in the first year may somehow contribute to adverse lipid profile and BMI in adulthood altering the expected association with insulin resistance when we use SPISE.

Studies on the epidemiology of nutritional status have focused much more attention on weight than on height, however, when it is alone, the height has been associated with several outcomes [45]. The results of our study support the hypothesis that growth in childhood would produce hepatic metabolism adjustment, demonstrated by the negative association of conditional linear growth with SPISE, which may be a marker linking early growth with adult determinant of type 2 diabetes mellitus.

The main strength of our study is the availability of data from two population-based birth cohorts, in the same location, born in different decades and periods of epidemiological transition. Thus far, there are few studies in countries with accelerating nutritional transition that have examined the relative significance of birth weight, nutritional status, and successive periods of weight and length gain in early life on markers of type 2 diabetes mellitus in young adults.

Nonetheless, some limitations should be considered; (1) the small sample size may have reduced statistical power to detect the minimum mean and regression coefficients differences of outcome variables; (2) we cannot rule out the possibility of selection bias due to missing data; (3) our main results are restricted to subjects with complete information on growth measurements at birth, at first year and at 22-28 years of age, further measurements between these ages were not available in our study, and therefore we had limited ability to determine associations with specific age periods of growth, such as the BMI rebound and weight gain during adolescence; (4) we assumed that health records were the gold standard for birthweight and weight and length in the first year, but these record might have some errors. However, in a Colombian study, which aimed to examine the validity of child birthweight recall by mothers, only 33% of mothers recalled their children's birthweights exactly as they appeared in hospital records [46]. Although, apparently, health records are a better option than recall, and it should be used with caution in epidemiological studies because there is a significant gap between the data that are captured during routine clinical care and the structured data needed for secondary analyses [47].

To sum up, we observed normal distributions of glycemia and prevalence of IFG and type 2 diabetes mellitus, but high insulin resistance, a consistent association with underweight, overweight, and conditional relative weight gain. In conclusion, interventions to improve the growth in children with stunting, at risk of wasting or with slow weight gain during the first year can prevent the onset of high level of glycemia in a large proportion of young adults. Based on the perspective of public health, it is important not only to consider nutritional status at one time but also to apply complementary methods to analyze growth trajectories, considering the strong correlation between repeated measurements over time and determinants of type 2 diabetes mellitus. The findings about SPISE suggest that more research is needed to understand the role of early nutritional status and growth on levels of this indicator, this possibility would be tested by analyses of cohorts addressing outcomes related to body composition, glucose concentrations, and lipid profiles.

Contributors

I. Pereyra conceived the study, collected literature, analyzed data, drafted the article and wrote the manuscript, and approved its final version. S. López-Arana made substantial contributions to the analysis and interpretation of data, revised the article critically for significant intellectual content, and approved the final version to be published. B. L. Horta made substantial contributions to the conception and design, assisted in data interpretation, provided expertise related to the cohort study, and epidemiological approaches and approved the final manuscript.

Additional information

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Resumen

El objetivo de este estudio fue evaluar si el peso, longitud y crecimiento condicionado durante el primer año está asociado con la glucemia y resistencia a la insulina entre adultos jóvenes. En el estudio se usó un diseño longitudinal no concurrente. Se trata de un estudio de cohorte con base poblacional, compuesto por individuos con una edad comprendida entre los 22 y 28 años de edad. Estimamos un puntaje z desde el nacimiento hasta el primer año y los niños fueron clasificados como: talla baja, con bajo peso, con sobrepeso, obesos, emaciados y con riesgo de emaciación, usando los cortes propuestos por la Organización Mundial de la Salud (Child Growth Standards, 2006*). Se estimaron como variables tanto el aumento de peso condicionado, como la longitud. La glucemia, insulina, el modelo de homeostasis para evaluar la resistencia a la insulina (HOMA, en inglés) y el estimador de sensibilidad a la insulina de un solo punto (SPISE, en inglés) fueron evaluados en la etapa adulta. Usamos regresiones múltiples lineales que incluyen las variables significativamente asociadas con la glucemia y resistencia a la insulina. Se evaluaron a 1.070 individuos, la glucemia en la etapa adulta fue mayor entre individuos que estaban emaciados o con riesgo de emaciación a los 12 meses (coeficiente β = 2,77; IC95%: 0,37; 5,21). En relación con el peso normal, estos individuos que sufrían sobrepeso a los 12 meses mostraron la más baja glucemia (coeficiente β = -2,39; IC95%: -4,32; -0,36). El aumento de peso condicionado durante el primer año estuvo negativamente asociado con la glucemia en la etapa adulta (β coeficiente = -0,65; IC95%: -1,23; -0,08). El SPISE fue más alto entre los individuos con bajo peso, y estuvo negativamente asociado con el aumento relativo de peso condicionado y el crecimiento lineal condicionado durante el primer año. En conclusión, descubrimos que la desnutrición y crecimiento insuficiente estuvieron asociados con una glucemia más alta.*

Diabetes Mellitus Tipo 2; Resistencia a la Insulina; Adulto Joven; Crecimiento

Resumo

O estudo teve como objetivo avaliar se o peso, estatura e crescimento condicional durante o primeiro ano de vida estão associados à glicemia e à resistência insulínica entre adultos jovens. O estudo usou um desenho longitudinal não concorrente. O estudo de coorte de base populacional analisou pessoas de idade entre 22 e 28 anos. Estimamos os escores-z desde o nascimento até o primeiro ano, e os lactentes foram classificados como: baixa estatura para idade, sobrepeso, obesidade, subnutrição e risco de subnutrição, usando os pontos de corte propostos pela Organização Mundial da Saúde (Child Growth Standards, 2006*). Foram estimadas as variáveis de peso condicional e ganho de estatura. Foram avaliadas na vida adulta a glicemia, insulina e avaliação do modelo de homeostase da resistência à insulina (HOMA-IR, em inglês) e estimador de sensibilidade à insulina de ponto único (SPISE, em inglês). Utilizamos regressão linear multivariada, incluindo as variáveis com associação significativa com a glicemia e a resistência insulínica. Foram avaliados 1.070 indivíduos, e a glicemia na idade adulta foi maior naqueles com subnutrição ou riso de subnutrição aos 12 meses de idade (coeficiente β = 2,77; IC95%: 0,37; 5,21). Em relação ao peso normal, indivíduos com sobrepeso aos 12 meses mostraram a menor glicemia (coeficiente β = -2,39; IC95%: -4,32; -0,36). O ganho ponderal condicional no primeiro ano de vida mostrou associação negativa com glicemia na vida adulta (coeficiente β = -0,65; IC95%: -1,23; -0,08). O SPISE foi mais alto entre indivíduos subnutridos e mostrou associação negativa com o ganho ponderal condicional e o crescimento linear condicional no primeiro ano. Como conclusão, o estudo mostrou que a subnutrição e o crescimento baixo estiveram associados a glicemia mais elevada.*

Diabetes Mellitus Tipo 2; Resistência à Insulina; Adulto Jovem; Crescimento

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