Preventive Medicine Reports 12 (2018) 298–303

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Impact of gaining or maintaining excessive weight in infancy on markers of metabolic homeostasis in young children: A longitudinal study in Chilean children

Fabian Vasquez, Camila Corvalan, Ricardo Uauy, Juliana Kain*

Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile

ARTICLE INFO

Keywords:
Longitudinal study
Children
Nutritional status
Excess weight
Metabolic homeostasis

ABSTRACT

Childhood obesity in Chile is one of the highest in the world. The objective of this study was to assess the impact of excessive weight gained or maintained over a 3-year period, on markers of metabolic homeostasis in young children. This is a longitudinal study which includes 243 children followed from 4 to 7 years. We assessed BMI, body fat percentage, waist circumference (WC), waist-hip ratio (WHR), waist-height (WH) and trunk fat as well as the following metabolic parameters: glucose, insulin, triglycerides, total cholesterol, LDL, HDL and metabolic risk score. Kruskal- Wallis was used to assess differences in metabolic markers by nutritional status and logistic regression to determine the effect of maintaining or gaining excess weight over the 3-year period, compared with children who maintained a normal weight. Children who were obese at both ages compared with those who were normal weight, had a significantly higher WC, serum concentrations of total fat, total cholesterol, triglycerides, LDL cholesterol and metabolic risk score ($P < 0.05$). Children who were overweight or obese at 4 and 7 years, had a greater risk of having a high WC (OR: 3.37; $P = 0.03$), total cholesterol (OR: 4.17; $P < 0.003$), triglycerides (OR: 1.96; $P = 0.04$); thus a higher metabolic risk score (OR: 3.21; $P = 0.003$). Excess weight maintained over time in early childhood, significantly increases the risk of having higher serum biomarkers of cardiovascular risk, which in turn determines the magnitude of cardiovascular and metabolic risks later in life.

1. Introduction

Obesity in early childhood is a public health problem in virtually all countries except for sub Saharan Africa and South Asia. It has been shown that it is associated with early onset type 2 diabetes and atherogenic processes that predispose young people to chronic diseases (Yeste and Carrascosa, 2011; Sinaiko, 2012). Cohort studies in adults show that these conditions individually or grouped under the definition of the Metabolic Syndrome (MS), determine an increased risk of cardiovascular disease (myocardial infarction, stroke, sudden death) and early mortality (Sinaiko, 2012; Poyrazoglu et al., 2014). Studies assessing tracking of adiposity into adulthood show that magnitude of the effect is dependent on the age of onset (Rolland-Cachera et al., 1987; Power et al., 1997). An early adiposity rebound recorded in most obese subjects suggests that factors promoting body fat accumulation operate early in life (Rolland-Cachera et al., 1987; Rolland-Cachera et al., 2006). Recent evidence on the relationship between child and adolescent obesity and adult adiposity shows significant tracking of early adiposity, suggesting that the increased cardiovascular risk of adult obesity may be mediated by childhood weight status (Power et al., 1997; Freedman et al., 2001; Freedman et al., 2007).

Adipose tissue is actively involved in regulating metabolic homeostasis and physiological functions such as immunity and inflammation. Adipose tissue produces and secretes adipokines (leptin, adiponectin, resistin, visfatin) and cytokines mainly tumor necrosis factor alpha, interleukin-6 and inflammatory proteins. Increase in cytokines release either as adipokines or by macrophages infiltrating adipose tissue, leads to chronic inflammation. This phenomenon plays a central role in the development of insulin resistance and type 2 diabetes mellitus, and explains the increased risk of cardiovascular disease associated with obesity (Pearson et al., 2003; Blankenberg et al., 2003; Antuna-Puente et al., 2008). These novel biomarkers may be stronger than conventional measures of lipoprotein concentrations as risk factors to predict future cardiovascular events. This provides an opportunity to assess the various causal pathways to take preventive action, focusing on early stages of the life course (Pearson et al., 2003; Blankenberg et al., 2003;

* Corresponding author at: Institute of Nutrition and Food Technology (INTA), University of Chile, 56-2-29781453, Av. El Líbano 5524, Macul, Santiago 7830490, Chile.
E-mail address: jkain@inta.uchile.cl (J. Kain).

https://doi.org/10.1016/j.pmedr.2018.10.004
Received 14 September 2018; Received in revised form 4 October 2018; Accepted 14 October 2018
Available online 23 October 2018

Antuna-Puente et al., 2008; Steinberger et al., 2009).

Unhealthy lifestyles associated with an increased intake of a high fat/ sugar diet, low physical activity and caloric imbalance, have shown to promote the development of cardiovascular and metabolic diseases (Hamilton et al., 2007; Lloyd-Jones et al., 2010). Hence, the contribution of adiposity "per se" to overall later life cardiometabolic risk in children remains uncertain. Therefore, the aim of this study was to assess the impact of excessive weight gained during infancy and/or maintained over a 3-year period (4 to 7 years of age) on metabolic markers of glucose and fat homeostasis in young children.

2. Materials and methods

2.1. Subjects

The sample included 243 children, from the Growth and Obesity Chilean Cohort Study (GOCS), whose initial objective was to evaluate the interaction between the rate of infant growth (changes in size and BMI between birth and 2 years) and family history of obesity, on adiposity (measured by both BMI and body fat percentage) of 1196 preschool children (4 years old) born with normal birth weight. The present study plan is to follow this cohort to adolescence.

The children included in the present report were selected randomly from the GOCS population at 4 years of age. Anthropometric measures and metabolic parameters were measured in 104 girls and 139 boys at 4 and 7 years, thus all were followed for 3 years. A signed informed consent was obtained from one of the parents or legal guardian. The Ethics Committee of the Institute of Nutrition and Food Technology (INTA), University of Chile, which meets national and international standards, approved the study.

2.2. Anthropometric measurements

Two trained experienced nutritionists using standardized procedures, measured weight, height, waist, circumference hip and triceps, biceps, subscapular and suprailiac skinfold thicknesses. Weight (kg) and height (cm) were measured in the morning, with minimal clothing (underwear only) with children standing on a portable electronic scale (Seca 770, SECA ®, Hamburg, Germany), with capacity up to 200 kg and accuracy of 10 g. Height was measured with a portable stadiometer (Harpenden 603; Holtain Ltd., Crosswell, UK) with a scale of 1 to 200 cm. and accuracy of 0.5 cm. WC (cm) was measured over the rim of the iliac crest, through the umbilicus. Hip circumference (cm) was measured in standing position, at the widest part of the gluteal region, at the level of the greater trochanter using an non-extensible metal, self-locking tape (Lufkin W606 PM; Cooper Tools, Raleigh, North Carolina), with accuracy of 0.1 cm. Skinfold thicknesses (mm) (biceps, triceps, subscapular and suprailiac) were measured with a millimeter precision Lange Caliper (1 mm) (Lohman et al., 1984). These skinfolds were used to determine total body fat using anthropometric models (Velásquez et al., 2008; Aguirre et al., 2015). The intra-observer technical error of measurement and mean observer bias were within the limits suggested by the World Health Organization (WHO, 2006a).

2.3. Blood samples

A trained nurse collected a sample of fasting venous blood (25 ml) of children. Mothers were contacted the day before to confirm the absence of fever (> 37.5 °C) or symptoms of acute infection in children as well as to remind them that the children had to fast the following morning. These conditions were re-checked by the nurse at the time of blood drawing, and exams were rescheduled in conditions were not met. Blood samples were analyzed at the Nutrition Laboratory at the Catholic University Medical Center. This laboratory conducts daily assessments of the accuracy of the measurements using quality control software's (Bio-Rad Laboratories Inc., Hercules, CA) and lipid measurements, and it has a Certificate of Traceability periodically updated by the Centers for Disease Control and Prevention (CDC) (Rudolf et al., 2004; Warolin et al., 2014). Serum glucose levels were measured using enzymatic colorimetric techniques (HUMAN; Gesellschaft für Diagnose und Biochemical, Wiesbaden, Germany) and serum insulin was measured with a radioimmunoassay kit (Linco Research Inc., St. Charles, MO). The HOMA-IR was calculated as fasting glucose (mmol/L) × fasting insulin (mU/ml)/22.5. Total cholesterol and triglycerides were measured using enzymatic colorimetric techniques (HUMAN). HDL was isolated by precipitation with a solution of sodium phosphotungstate magnesium chloride (Seigler and Wu, 1981). LDL cholesterol was calculated using the Friedewald formula (i.e., all concentrations of triglycerides were < 400 mg/dl) (Friedewald et al., 1972).

2.4. Anthropometric indices

BMI was estimated as kg/m^2. Standard scores (z score) of weight for age (WAZ), height for age (HAZ), and BMI-for- age (BAZ) were estimated comparing values with the WHO reference 2006 (WHO, 2006b). Normal nutritional status was defined as ($-1 \geq$ BAZ $<$ 1), overweight as ($1 \leq$ BAZ ≤ 2) and obesity as (BAZ $>$ 2 SD). Central obesity: Boys WC ≥ 90th percentile in 4 years (57.6122 cm) and 7 years (67.8 cm). Girls: WC ≥ 90th percentile in 4 years (58.3 cm) and 7 years (67.5 cm) (Fernandez et al., 2004). WC divided by height and hip circumference was used to calculate the WH and WHR, respectively. Triceps, biceps, subscapular and suprailiac and the abdominal, subscapular and suprailiac thicknesses were used to estimate total body fat and body fat trunk, respectively. In order to estimate the percentage of body fat at 4 and 7 years, we used predictive equations, calculated for Chilean children. At 4 years (Velásquez et al., 2008), the following predictive equation was used: [−1.524 + (0.371 ∗ weight kg) + 0.114 ∗ (triceps thicknesses mm + subscapular thicknesses mm) − (0,238 ∗ age years) + (0.378 ∗ gender 1 boys, 2 girls) − (0.105 ∗ calf circumference)] while at 7 years we used a prediction equation previously developed in a subsample of 7–9 years old children from this same cohort and validated by deuterium dilution (Aguirre et al., 2015). This equation is: (1.826 ∗ ZBMI) + (0.783 ∗ triceps skinfold) + (0.3073 ∗ biceps skinfold) + 15.558, against 3C model ($R^2 = 0.78$).

2.5. Metabolic risk factors

The cutoff points used to define abnormal cardiometabolic status were: glucose concentration ≥ 100 mg/dl (American Diabetes Association, 2006); HOMA-IR ≥ 3.2 (Kurtoglu et al., 2005); total cholesterol, LDL cholesterol and triglycerides ≥ 95th percentile [American Academy of Pediatrics: girls (total cholesterol ≥ 197 mg/dl, LDL cholesterol ≥ 140 mg/dl and triglycerides ≥ 120 mg/dL) and boys (total cholesterol ≥ 186 mg/dl, LDL cholesterol ≥ 129 mg/dl, and triglycerides ≥ 85 mg/dl) (Daniels, Greer and Committee on Nutrition, 2008); HDL cholesterol ≤ 5th centile [American Academy of Pediatrics: girls (38 mg/dL) and boys (36 mg/dL) (Zimmet et al., 2007). Metabolic syndrome risk score was determined by adding the standardized Z scores for waist circumference, glucose, insulin, triglycerides and inverse HDL-cholesterol dividing the sum by 5 (Brage et al., 2004; Zimmet et al., 2007).

2.6. Statistical analyses

Mean values and standard deviations were calculated for continuous and frequency distributions for categorical variables. Student test was used to assess differences in continuous and Chi-square and Fisher's exact tests for categorical variables. Student *t* test was also used to compare differences in metabolic variables by sex and nutritional status at 4 and 7 years and Chi-square and Fisher's exact test to compare the prevalence of metabolic markers at 4 and 7 years for both sexes.

Based on the changes of the children's nutritional status over the 3-

Table 1
Anthropometric characteristics of the sample by age and sex.[a]

Variable	4 years			7 years		
	Boys (n = 139)	Girls (n = 104)	*P* value[b]	Boys (n = 139)	Girls (n = 104)	*P* value[b]
Age (years)	4.25 ± 0.3[c]	4.27 ± 0.3	0.64	6.95 ± 0.4	6.94 ± 0.4	0.87
Weight (kg)	17.7 ± 2.3	17.9 ± 2.8	0.52	25.5 ± 4.8	25.7 ± 4.9	0.81
Weight-for-age z score	0.31 ± 0.9	0.38 ± 1.0	0.56	0.67 ± 1.2	0.73 ± 1.0	0.63
Height (cm)	103.7 ± 4.1	103.9 ± 4.5	0.67	121.9 ± 4.9	121.9 ± 5.2	0.99
Height-for-age z score	−0.27 ± 0.9	−0.17 ± 0.9	0.40	0.11 ± 0.9	0.27 ± 0.9	0.19
BMI (kg/m^2)	17.7 ± 2.3	17.9 ± 2.8	0.52	17.1 ± 2.4	17.2 ± 2.6	0.71
BMI-for-age z score (BAZ)	0.73 ± 1.0	0.71 ± 1.1	0.90	0.82 ± 1.3	0.77 ± 1.1	0.73
Hip (cm)	56.5 ± 3.9	58.1 ± 4.5	< 0.001	65.6 ± 6.0	66.8 ± 5.6	0.10
Waist-to-hip ratio	0.93 ± 0.0	0.90 ± 0.0	< 0.0001	0.90 ± 0.0	0.88 ± 0.0	< 0.001
Waist-to-height ratio	0.51 ± 0.0	0.51 ± 0.0	0.83	0.48 ± 0.1	0.48 ± 0.1	0.97
Sum of 4 skinfold (mm)[e]	24.2 ± 8.9	30.8 ± 13.9	< 0.0001	25.9 ± 10.0	30.7 ± 12.0	< 0.0001
Truncal fat (mm)[f]	20.9 ± 8.2	26.7 ± 13.7	< 0.0001	23.1 ± 10.4	27.4 ± 11.2	< 0.001
Total fat (%)	19.3 ± 3.8[g]	22.8 ± 6.6[g]	< 0.0001	24.5 ± 4.9[h]	25. 7 ± 5.0[h]	0.08
Body fat index (kg/m^2)	3.2 ± 0.9	3.8 ± 1.5	< 0.0001	4.3 ± 1.6	4.5 ± 1.6	0.26
Normal weight[a]	66.2 (92)[d]	68.3 (71)[d]	0.77	62.6 (87)[d]	66.4 (69)[d]	0.62
Overweight/obese[a]	33.8 (47)[d]	31.7 (33)[d]	0.73	37.4 (52)[d]	33.6 (35)[d]	0.72

[a] WHO 2006, World Health Organization; NHANES III, National Health and Nutrition Examination Survey.
[b] Sex differences assessed by using Student's *t*-test or chi-square test.
[c] Values expressed as mean ± SD: standard deviation.
[d] Values expressed as (% (n)).
[e] Calculated by summing biceps, triceps, suprailiac and subscapular skinfold thicknesses.
[f] Calculated by summing abdominal, suprailiac and subscapular skinfold thicknesses.
[g] Estimated on the basis of a predictive equation that uses age, sex, weight, calf circumference and triceps and subscapular skinfold thicknesses.
[h] Estimated on the basis of a predictive equation that uses BMIZ, biceps and triceps skinfold thicknesses.

year period, we defined 4 groups: normal to normal (N-N), overweight/obese to normal (OW-N), normal to overweight/obese (N-OW) and obese to obese (OB-OB). We used Kruskal-Wallis to analyze differences between groups and the post-hoc analysis (Bonferroni test) to determine which groups were different.

To evaluate the effect of maintaining an excess weight and/or gaining weight over the 3-year period compared with children of normal nutritional status, we used multiple logistic analysis, estimating OR with 95% confidence interval, for metabolic risk.

A *P* value of < 0.05 was considered statistical significant. Analyses were performed using STATA version 12.0 (StataCorp 2011 Stata Statistical Software. Release 12 College Station, TX. StataCorp LP.)

3. Results

Anthropometric characteristics of the sample by age and sex are presented in Table 1. 243 children (57% boys) were included in this study. At 4 years, girls had a significantly greater hip circumference and adiposity (assessed by the sum of skinfolds), body fat index and total body fat ($P < 0.001$) as well as more truncal fat ($P < 0.0001$), while boys had a significantly higher WHR ($P < 0.0001$). At 7 years, there was a significantly greater WHR in boys ($P < 0.001$) and increased adiposity ($P < 0.0001$) and trunk fat ($P < 0.001$) in girls.

Metabolic characteristics of the sample by sex and age between 4 and 7 years are shown in Table 2. In boys, at 7 years (compared with values at 4 years), WC, fasting glucose, HDL-cholesterol and triglycerides were significantly higher ($P < 0.001$), while girls had higher WC, fasting glucose, HDL-cholesterol, triglycerides and metabolic risk score ($P < 0.05$). However, in boys and girls at 4 years compared with 7 years, LDL-cholesterol and fasting insulin levels were significantly higher ($P < 0.05$). Both in boys and girls at 4 years, there was a significantly higher proportion of children with LDL-cholesterol and HDL-cholesterol above cutoff points ($P < 0.05$). At 7 years, there was only a higher proportion of boys with triglycerides above cutoff points ($P < 0.001$).

Mean concentrations of metabolic markers by nutritional status and age are presented in Table 3. As expected, at 4 and 7 years, overweight/obese (OW) children had higher mean values of total fat, WC, metabolic risk score and fasting insulin, when compared with normal weight children at both ages (N) ($P < 0.05$), while additionally at 7 years, mean concentrations of HOMA-IR, total cholesterol, LDL-cholesterol and triglycerides ($P < 0.05$) were also significantly higher in those children.

Table 4 shows the mean concentrations of cardiometabolic risk factors in children who maintained or changed their nutritional status from 4 to 7 years. In children who increased their weight so as to change their nutritional status, significant increases were found in BAZ, total fat (%), WC, total cholesterol, triglycerides, LDL-cholesterol and metabolic score syndrome ($P < 0.05$). In addition, when comparing children by categories of nutritional status, statistically significant differences were observed in total fat (%), WC, total cholesterol, LDL cholesterol, triglycerides and metabolic score among them ($P < 0.05$). In the comparison of N-N with N-OW and OW-N with N-OW, significant differences were observed in total fat, WC and metabolic risk score.

Table 5 shows a multiple logistic regression model for the association between the presence of metabolic risk and change in the nutritional status, from 4 to 7 years, compared to those who were normal weight at both ages, adjusted for sex and age. We observed that children, who increased in weight over the 3 years as well as obese children at both ages (OB-OB), deteriorated their metabolic profile when compared to with children who remained N-N. That is, OW-N lowered their probability of presenting metabolic risk (OR: 0.34); while N-OW increased this probability (OR: 4.07, $P < 0.004$), and more so OB-OB (OR: 8.39, $P \leq 0.001$).

4. Discussion

In a contemporary cohort of Chilean children with a three year follow-up (4 to 7 years), we found that overweight and obesity in young children are associated with disruption of metabolic homeostasis reflected specifically by increased total fat, WC, HOMA-IR, total cholesterol, LDL cholesterol, triglycerides, fasting insulin and metabolic risk score ($P < 0.05$). Children who were overweight or obese at 4 and 7 years, showed a significant deterioration of their cardiometabolic profile. These results are similar to those obtained in a cohort of Korean children (n = 109, mean age 10.5 ± 0.4 y), evaluated after a two year

Table 2
Metabolic characteristics of the sample at 4 and 7 years, by sex and age.

Variable				Above cutoff points % (n)[a]		
	4 years[d]	7 years[d]	*P* value[b]	4 years[e]	7 years[e]	*P* value[c]
Boys (n = 139)						
Waist circumference (cm)	52.5 ± 3.5	58.9 ± 6.7	< 0.001	9.4 (13)	11.5 (16)	0.56
Fasting glucose (mg/dL)	80.8 ± 9.1	90.8 ± 6.3	< 0.001	3.6 (5)	7.4 (10)	0.17
HOMA-IR	1.31 ± 0.6	1.22 ± 0.4	0.16	2.2 (3)	0.7 (1)	0.33
Total cholesterol (mg/dL)	163.2 ± 26.6	167.8 ± 26.3	0.09	19.4 (27)	26.7 (36)	0.15
LDL cholesterol (mg/dL)	111.4 ± 25.2	97.3 ± 27.6	< 0.001	23.7 (33)	13.0 (17)	0.02
HDL cholesterol (mg/dL)	36.4 ± 9.5	50.2 ± 15.4	< 0.001	54.7 (76)	18.9 (25)	< 0.001
Triglycerides (mg/dL)	77.3 ± 30.5	102.7 ± 52.6	< 0.001	30.9 (43)	54.8 (74)	< 0.001
Fasting insulin (μU/mL)	6.4 ± 2.4	5.4 ± 1.4	< 0.001	–	–	–
Metabolic risk score[6]	0.01 ± 0.5	0.12 ± 0.4	0.02	23.7 (33)	28.2 (38)	0.41
Girls (n = 104)						
Waist circumference (cm)	52.6 ± 4.4	58.9 ± 6.8	< 0.001	12.5 (13)	14.4 (15)	0.68
Fasting glucose (mg/dL)	77.3 ± 6.6	89.9 ± 5.9	< 0.001	1.0 (1)	4.1 (4)	0.15
HOMA-IR	1.27 ± 0.7	1.30 ± 0.6	0.74	1.9 (2)	3.1 (3)	0.60
Total cholesterol (mg/dL)	169.4 ± 25.8	172.6 ± 26.4	0.28	14.4 (15)	15.3 (15)	0.86
LDL cholesterol (mg/dL)	114.1 ± 26.5	104.9 ± 30.7	0.002	16.4 (17)	9.2 (9)	0.13
HDL cholesterol (mg/dL)	37.8 ± 9.8	50.4 ± 12.3	< 0.001	50.5 (52)	14.3 (14)	< 0.001
Triglycerides (mg/dL)	88.6 ± 32.9	98.2 ± 50.8	0.04	17.3 (18)	26.5 (26)	0.11
Fasting insulin (μU/mL)	6.5 ± 2.6	5.88 ± 2.5	0.05	–	–	–
Metabolic risk score[f]	−0.06 ± 0.6	0.09 ± 0.6	0.04	29.8 (31)	22.5 (22)	0.23

[a] Cutoff points for risk factors were the following: 4 years: boys: waist circumference 90th percentile = 57.6 cm. Girls: waist circumference 90th percentile = 58.3 cm. 7 years: Boys: 90th percentile = 67.8 cm. Girls: 90th percentile = 67.5 cm; glucose ≥ 100 mg/dL; HOMA-IR ≥ 3.2; total cholesterol, LDL cholesterol and triglycerides ≥ 95th percentile [American Academy of Pediatrics: girls (total cholesterol ≥ 197 mg/dL. LDL cholesterol ≥ 140 mg/dL and triglycerides ≥ 120 mg/dL) and boys (total cholesterol ≥ 186 mg/dL. LDL cholesterol ≥ 129 mg/dL and triglycerides ≥ 85 mg/dL)]; and HDL cholesterol ≤ 5th percentile [American Academy of Pediatrics: girls (38 mg/dL) and boys (36 mg/dL)].
[b] Age differences assessed by Paired Student's *t*-test.
[c] Age differences assessed by Chi-square or Fisher's exact test.
[d] Values expressed as Mean ± SD.
[e] Values expressed as (% (n)).
[f] Metabolic risk score: SDS (waist circumference + glucose + insulin + triglycerides − HDL-cholesterol / 5).

follow-up, to assess the relationship of childhood obesity with insulin resistance and MS. Obese children (n = 46) showed a significantly higher percentage of body fat and WC compared to those with normal weight ($P < 0.0001$). In addition, obese subjects had significantly higher triglyceride levels ($P < 0.0001$), insulin ($P < 0.0001$) and HOMA-IR ($P < 0.0001$) (Lee et al., 2015). Consistent with these results, a study of 233 British children, followed for nine years from birth, also found that those who were overweight or obese at 9 year had higher levels of HOMA-IR, triglycerides, and excessive weight gain from 5 to 9 years (Gardner et al., 2009).

A study including 424 in Chinese children recruited at 5 years and followed until age 10 concluded that children with greater than normal changes in weight for height during that period compared to those with normal changes, showed significantly higher cardiovascular risk factors (insulin, HOMA-IR, systolic and diastolic blood pressure and triglycerides) (Chen et al., 2011).

Our findings suggest that the risk of MS and specifically a high C-reactive protein is significantly higher in children with overweight and obesity, underlying the harmful effect of increased body fat in this age group. Weiss R, et al. in their study of 439 obese American children and adolescents found similar results to evaluate the effect of different degrees of obesity in the prevalence of MS and its relation to insulin resistance (Weiss et al., 2004). Results from the study showed that the prevalence of MS increased with the severity of obesity. Each half-unit increase in BMI, converted to a z score was associated with an increased risk of MS among overweight and obese subjects (OR, 1.55; CI, 1.16 to 2.08).

Table 3
Mean concentrations of metabolic variables by nutritional status at 4 and 7 years (BAZ; World Health Organization, 2006a).[a]

Variable	4 years (n = 243)			7 years (n = 243)		
	Normal weight (n = 163)	Overweight/obese (n = 80)	*P* value[b]	Normal weight (n = 156)	Overweight/obese (n = 87)	*P* value[b]
BAZ	0.14 ± 0.6	1.91 ± 0.8	< 0.001	0.04 ± 0.7	2.1 ± 0.6	< 0.001
Total fat (%)	19.0 ± 4.3	24.4 ± 5.8	< 0.001	22.0 ± 2.2	30.5 ± 3.8	< 0.001
Waist circumference (cm)	50.9 ± 2.6	56.0 ± 3.9	< 0.001	55.1 ± 3.3	65.8 ± 5.7	< 0.001
Fasting glucose (mg/dL)	78.1 ± 6.7	80.0 ± 8.8	0.09	89.9 ± 6.0	91.4 ± 6.1	0.08
HOMA-IR	1.26 ± 0.6	1.36 ± 0.8	0.27	1.17 ± 0.2	1.41 ± 0.8	< 0.001
Total cholesterol (mg/dL)	165.1 ± 27.0	167.7 ± 26.6	0.47	166.0 ± 24.9	176.7 ± 27.7	0.003
LDL cholesterol (mg/dL)	111.2 ± 26.5	114.7 ± 25.2	0.33	96.9 ± 25.3	106.0 ± 34.21	0.02
HDL cholesterol (mg/dL)	37.3 ± 10.1	36.6 ± 9.2	0.62	50.8 ± 14.6	49.4 ± 13.5	0.48
Triglycerides (mg/dL)	82.6 ± 32.9	82.2 ± 34.2	0.93	91.4 ± 41.2	117.7 ± 63.8	0.002
Fasting insulin (μU/mL)	6.3 ± 2.1	7.0 ± 3.2	0.04	5.3 ± 0.6	6.2 ± 3.0	< 0.001
Metabolic risk score[c]	−0.1 ± 0.5	0.2 ± 0.6	< 0.001	−0.1 ± 0.3	0.5 ± 0.4	< 0.001

[a] WHO 2006. World Health Organization; NHANES III. Third National Health and Nutrition Examination Survey.
[b] Nutritional Status differences assessed by Student's *t*-test.
[c] Metabolic risk score: SDS (waist circumference + glucose + insulin + triglycerides − HDL-cholesterol / 5).

Table 4
Cardiometabolic characteristics of the sample in children who maintained or changed their nutritional status between 4 and 7 years.

	N-N (n = 132)	OW-N (n = 24)	N-OW (n = 31)	OB-OB (n = 56)	*P* value[a]
BAZ	−0.07 ± 0.7[b,c,d]	0.67 ± 0.2[b,e]	1.57 ± 0.6[c]	2.47 ± 0.6[d,e]	< 0.001
Total fat (%)	21.7 ± 2.2[b,c]	23.3 ± 1.2[d,e]	28.4 ± 3.1[b,d]	31.7 ± 3.6[c,e]	< 0.001
Waist circumference (cm)	54.8 ± 3.3[b,c]	56.4 ± 3.2[d,e]	62.6 ± 4.3[b,d]	67.6 ± 5.5[c,e]	< 0.001
Fastin glucose (mg/dL)	90.3 ± 6.0	88.0 ± 5.9	91.6 ± 6.0	91.2 ± 6.2	0.15
HOMA-IR	1.17 ± 0.2	1.14 ± 0.2	1.18 ± 0.2	1.54 ± 1.0	0.07
Total cholesterol (mg/dL)	166.4 ± 24.5[b]	163.9 ± 27.1[c]	168.1 ± 23.7	181.5 ± 28.8[b,c]	0.01
Triglycerides (mg/dL)	91.1 ± 39.7[b]	92.9 ± 49.3	104.8 ± 45.9	125.0 ± 71.3[b]	0.01
HDL cholesterol (mg/dL)	49.5 ± 14.2	57.6 ± 14.9	48.2 ± 12.4	50.1 ± 14.1	0.05
LDL cholesterol (mg/dL)	98.6 ± 24.9	87.7 ± 25.3[b]	99.0 ± 25.7	110.1 ± 37.9[b]	0.03
Fastin insulin (μU/mL)	5.3 ± 0.6	5.3 ± 0.7	5.2 ± 0.5	6.7 ± 3.7	0.29
Metabolic risk score	−0.1 ± 0.3[b,c]	−0.2 ± 0.3[d,e]	0.2 ± 0.3[b,d]	0.6 ± 0.7[c,e]	< 0.001

N: Normal to normal (N-N); overweight/obese to normal (OW-N); normal to overweight/obese (N-OW) and obese-obese (OB-OB).
[b,c,d,e]Equal numbers indicate significant differences between groups (post-hoc Bonferroni) ($P < 0.05$).
[a] Nutritional Status differences assessed by Kruskal-Wallis.

Table 5
Multiple logistic regression model for the association of metabolic risk with change in nutritional status, adjusted by sex and age.[a]

Variable	OR[b]	SE[c]	(95% CI)[d]	*P* value
Initial metabolic risk	3.08	1.15	1.48 6.41	0.003
Change in nutritional status				
OW-N	0.34	0.37	0.04 2.78	0.31
N-OW	4.07	1.98	1.57 10.57	0.004
OB-OB	8.39	3.38	3.81 18.49	< 0.001
Sex	0.73	0.27	0.36 1.49	0.39
Age	2.48	1.21	0.95 6.48	0.06

[a] Logistic regression model. Hosmer-Lemeshow ($P = 0.5810$) indicated that the goodness of fit of the model is satisfactory.
[b] OR: odds ratio.
[c] SE: standard error.
[d] (95% CI): 95% confidence interval.

Based on our findings and compared with other longitudinal studies (Freedman et al., 2007; Baker et al., 2007), children who become normal weight, improve their metabolic parameters when compared with children who remain obese or overweight, or change from normal to overweight or obese. Other studies have also shown that change in adiposity predicts future metabolic risk (Freedman et al., 2007; Baker et al., 2007; Gardner et al., 2009; Chen et al., 2011) demonstrating that increase in body fat is an early indicator of cardiovascular risk and correlates directly with the magnitude and prevalence of cardiovascular and metabolic disorders (Geib et al., 2001; Cascella et al., 2006; Baker et al., 2007; Bacha et al., 2014). The excessive accumulation of body fat produces a high impact on the health of obese subjects, affecting their fitness, vitality and overall quality of life. These problems may persist into adulthood if there are not addressed early on (Stein and Colditz, 2004; Magnussen et al., 2013). Some authors argue that weight increase during childhood is the key determinant of future metabolic health of individuals (Ong et al., 2004; Ekelund et al., 2007).

It is important to acknowledge the improvement in anthropometric and metabolic parameters for overweight and obese children who lost weight over the 3-year period. Compared to children who gained weight or maintained their overweight status, that is, N-OW and OB-OB, the most significant improvements were observed in total body fat, WC and metabolic risk score. In general, studies that have addressed the impact that weight loss produces on metabolic variables include overweight children and in general are due to lifestyle interventions. Two systematic reviews examining the impact of lifestyle interventions on weight and cardiometabolic parameters in obese children found significant differences in LDL, triglycerides, fasting insulin and blood pressure, post-intervention (Ho et al., 2012; Ho et al., 2013).

An important strength of our study is that the data originates from a large cohort followed from age 3 years, enabling monitoring of the nutritional status and metabolic conditions of the children. There are limitations that should be acknowledged, the first one is the fact that we do not have information on the dietary habits and physical activity of the children in order to try to explain why the changes in their nutritional status occurred. Also, the proportion of children who changed their nutritional status over the 3 years was small.

5. Conclusions

Children who were overweight or obese as well those who maintained their overweight status between 4 and 7 years of age, showed a significant deterioration of their cardiometabolic profile. Maintaining an excess weight over time in early childhood may lead to cardiovascular risks that correlate directly with the presence and magnitude of cardiovascular and metabolic abnormalities.

Competing interests

The authors declare no conflicts of interest.

Authors' contributions

FV participated in data collection, obtained and interpreted the data set, and wrote the manuscript; CC initiated the study, assisted in interpretation of results and writing of the manuscript; RU initiated the study; JK assisted in interpretation of results and writing the manuscript.

Acknowledgements

This research was funded by FONDECYT (Postdoctoral Grant no. 3140344), FONDECYT (Grant no. 1090252) and FONDECYT (Grant no. 1120326). We would like to thank Professor Bárbara Leyton for assisting in the statistical analyses.

References

Aguirre, C.A., Salazar, G.D., Lopez de Romaña, D.V., Kain, J.A., Corvalán, C.L., Uauy, R.E., 2015. Evaluation of simple body composition methods: assessment of validity in prepubertal Chilean children. Eur. J. Clin. Nutr. 69, 269–273.
American Diabetes Association, 2006. Diagnosis and classification of diabetes mellitus. Diabetes Care 29, S43–S48.
Antuna-Puente, B., Feve, B., Fellahi, S., Bastard, J.P., 2008. Adipokines: the missing link between insulin resistance and obesity. Diabete Metab. 34, 2–11.
Bacha, F., Edmundowicz, D., Sutton-Tyrell, K., Lee, S., Tfayli, H., Arslanian, S.A., 2014. Coronary artery calcification in obese youth: what are the phenotypic and metabolic determinants? Diabetes Care 37, 2632–2639.
Baker, J.L., Olsen, L.W., Sorensen, T.I., 2007. Childhood body-mass index and the risk of coronary heart disease in adulthood. N. Engl. J. Med. 357, 2329–2337.
Blankenberg, S., Barbaux, S., Tiret, L., 2003. Adhesion molecules and atherosclerosis. Atherosclerosis 170, 191–203.

Brage, S., Wedderkopp, N., Ekelund, U., et al., 2004. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). Diabetes Care 27, 2141–2148.
Cascella, T., Giallauria, F., Tafuri, D., et al., 2006. Cardiovascular complications of obesity. Monaldi Arch. Chest Dis. 66, 270–274.
Chen, Y.Y., Lee, Y.S., Wang, J.P., et al., 2011. Longitudinal study of childhood adiposity and the risk of developing components of metabolic syndrome-the Da Qing children cohort study. Pediatr. Res. 70, 307–312.
Daniels, S.R., Greer, F.R., Committee on Nutrition, 2008. Lipid screening and cardiovascular health in childhood. Pediatrics 122, 198–208.
Ekelund, U., Ong, K.K., Linne, Y., et al., 2007. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J. Clin. Endocrinol. Metab. 92, 98–103.
Fernandez, J.R., Redden, D.T., Pietrobelli, A., Allison, D.B., 2004. Waist circumference percentiles in nationally representative samples of African-American, European-American, and the American-Arabs children and adolescents. J. Pediatr. 145, 439–444.
Freedman, D., Kettel-Khan, L., Dietz, W., Srinivasan, S., Berenson, G., 2001. Relationship of childhood obesity to coronary heart disease risk factors in adulthood. The Bogalusa Heart Study. Pediatrics 108, 712–718.
Freedman, D.S., Mei, Z., Srinivasan, S.R., Berenson, G.S., Dietz, W.H., 2007. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J. Pediatr. 150, e2–17.
Friedewald, W.T., Levy, R.I., Fredrickson, D.S., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18, 499–502.
Gardner, D.S., Hosking, J., Metcalf, B.S., Jeffery, A.N., Voss, L.D., Wilkin, T.J., 2009. Contribution of early weight gain to childhood overweight and metabolic health: a longitudinal study (EarlyBird 36). Pediatrics 123, e67–e73.
Geib, H.C., Parhofer, K.G., Schwandt, P., 2001. Parameters of childhood obesity and their relationship to cardiovascular risk factors in healthy prepubescent children. Int. J. Obes. 25, 830–837.
Hamilton, M.T., Hamilton, D.G., Zderic, T.W., 2007. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes 56, 2655–2667.
Ho, M., Garnett, S.P., Baur, L.A., et al., 2012. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. Pediatrics 130, e1647–e1671.
Ho, M., Garnett, S.P., Baur, L.A., et al., 2013. Impact of dietary and exercise interventions on weight change and metabolic outcomes in obese children and adolescents: a systematic review and meta-analysis of randomized trials. JAMA Pediatr. 167, 759–768.
Kurtoglu, S., Kendirci, M., Atabek, M.E., Yazici, C., 2005. Homeostasis model assessment is more reliable than the name fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics 115, e500–e503.
Lee, A., Jang, H.B., Ra, M., et al., 2015. Prediction of future risk of insulin resistance and metabolic syndrome based on Korean boy's metabolite profiling. Obes. Res. Clin. Pract. 9, 336–345.
Lloyd-Jones, D.M., Hong, Y., Labarthe, D., et al., 2010. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 121, 586–613.
Lohman, T.G., Boileau, R.A., Slaughter, R.A., 1984. Body composition in children. In: Lohman, T.G. (Ed.), Human Body Composition. Human Kinetics, New York, pp. 29–57.
Magnussen, C.G., Smith, K.J., Juonala, M., 2013. When to prevent cardiovascular disease? As early as possible: lessons from prospective cohorts beginning in childhood. Curr. Opin. Cardiol. 28, 561–568.
Ong, K.K., Petry, C.J., Emmett, P.M., et al., 2004. ALSPAC study team. Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. Diabetologia 47, 1064–1070.
Pearson, T.A., Mensah, G.A., Alexander, R.W., et al., 2003. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107, 499–511.
Power, C., Lake, J.K., Cole, T.J., 1997. Measurements and long-term health risks of child and adolescent fatness. Int. J. Obes. 21, 507–526.
Poyrazoglu, S., Bas, F., Darendeliler, F., 2014. Metabolic syndrome in young people. Curr. Opin. Endocrinol. Diabetes Obes. 21, 56–63.
Rolland-Cachera, M.F., Deheeger, M., Avons, P., Guilloud-Bataille, M., Patois, E., Sempé, M., 1987. Tracking adiposity patterns from 1 month to adulthood. Ann. Hum. Biol. 14, 219–222.
Rolland-Cachera, M.F., Deheeger, M., Maillot, M., Bellisle, F., 2006. Early adiposity rebound: causes and consequences for obesity in children and adults. Int. J. Obes. 30, S11–S17.
Rudolf, M.C., Greenwood, D.C., Cole, T.J., et al., 2004. Rising obesity and expanding waistlines in schoolchildren: a cohort study. Arch. Dis. Child. 89, 235–237.
Seigler, L., Wu, W.T., 1981. Separation of serum high-density lipoprotein cholesterol for determination: ultracentrifugation vs precipitation with sodium phosphotungstate and magnesium chloride. Clin. Chem. 27, 838–841.
Sinaiko, A.R., 2012. Metabolic syndrome in children. J. Pediatr. 88, 286–288.
Stein, C.J., Colditz, G.A., 2004. The epidemic of obesity. J. Clin. Endocrinol. Metab. 89, 2522–2525.
Steinberger, J., Daniels, S.R., Eckel, R.H., et al., 2009. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Circulation 119, 628–647.
Velásquez, M., Salazar, G., Vio, F., Díaz, N., Anziani, A., 2008. Validación de ecuaciones antropométricas para evaluar composición corporal en niños preescolares chilenos. Rev. Med. Chil. 136, 433–441.
Warolin, J., Coenen, K.R., Kantor, J.L., et al., 2014. The relationship of oxidative stress, adiposity and metabolic risk factors in healthy Black and White American youth. Pediatr. Obes. 9, 43–52.
Weiss, R., Dziura, J., Burgert, T.S., et al., 2004. Obesity and the metabolic syndrome in children and adolescents. N. Engl. J. Med. 350, 2362–2374.
World Health Organization, 2006a. WHO Child Growth Standards: Methods and Development: Length/Height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body Mass Index-for-age. WHO, Geneva, Switzerland.
World Health Organization, 2006b. Seeking Antenatal Care WHO Growth Reference Study Group. Reliability of anthropometric measurements in the WHO Growth Reference Study seeking antenatal care. Acta Paediatr. Suppl. 450, 38–46.
Yeste, D., Carrascosa, A., 2011. Obesity-related metabolic disorders in childhood and adolescence. An. Pediatr. (Barc.) 75 (135.e1-9).
Zimmet, P., Alberti, K.G., Kaufman, F., et al., 2007. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr. Diabetes 8, 299–306.