RESEARCH PAPER

The Influence of Fetal Growth Restriction on Cardiovascular Health among Adolescents in Brazil: *A Retrospective Cohort Study*

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Objective: To investigate whether fetal growth restriction is associated with changes in cardiovascular risk factors later in life.

Design: A retrospective cohort study.

Settings: Tertiary-care hospital serving urban population from the Brazilian Northeast.

Participants/patients: 172 adolescents aged 10-20 years were evaluated for the effects of fetal growth restriction on anthropometric measurements, blood pressure, lipids and fasting glucose and flow-mediated brachial artery dilatation.

Intervention: The adolescents' birth weight and their gestational age at birth were used to identify fetal growth restriction according to the 10th percentile and divided between exposed (<10th percentile) and not exposed (≥10th percentile). The Student-t test or the Mann-Whitney test and chi-square were used. The significance level was considered to be 0.05.

Main Outcome Measure(s): Current Anthropometric, metabolic and endothelial measures of subjects.

Results: The majority of the current anthropometric, metabolic and endothelial measures did not differ between groups. The unexposed group had a higher hip circumference (89.1 cm) and higher total cholesterol (196.4 mg/dL) than those exposed (85.4 cm, 136.9 mg/dL, respectively) (*P*=0.04).

Conclusions: In the sample studied, no association was found between fetal growth restriction and changes in cardiovascular risk factors in adolescents.

Keywords: *Cardiovascular disease, Fetal growth retardation, Gestational age, Risk factors.*

Small for gestational age (SGA) babies presently constitute 27% of live births worldwide [1,2]. In addition to the damage in infancy, such as an increased risk for mortality [3] and cognitive impairment [4], being born SGA is also associated with a higher prevalence of chronic diseases in adulthood [5-9]. Explanatory models for the association between intrauterine growth restriction and its effect on physiological processes are based on the reduced number of nephrons [10], altered arterial compliance [11] or fetal exposure to excess glucocorticoid [12] identified in these individuals.

Evidence shows that changes, such as increased blood pressure, can be identified early in children and adolescents who have suffered intrauterine constraint [13-16]. On the other hand, a growing number of studies have identified a positive association or lack of association between fetal growth restriction and some cardiovascular risk factors such as blood pressure [17], increased anthropometric measurements [9], endothelial dysfunction [18] and metabolic syndrome [19]. In low income countries, the nutritional recovery of children with fetal growth restriction seems to reduce morbidity and mortality [20], while in countries with higher incomes, it is associated with a higher prevalence of cardiovascular diseases [21].

We conducted this study to investigate whether fetal growth restriction is associated with changes in cardiovascular risk factors among urban individuals aged 10-20 years.

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Methods

This retrospective cohort study was conducted among a predominantly urban population in the Brazilian northeast. The Research Ethics Committee of the Assis Chateaubriand Maternity Teaching Hospital – Federal University of Ceará approved this study, by means of the protocol 197.298. The study was conducted between February and August 2013 and respected all ethical and legal guidelines for research on humans. An informed consent form was obtained from all participants or their legal guardians.

Information on newborn weight, length and birth conditions were taken from the hospital's birth records,

which give data on the day and hour of the birth. It was possible to select exposed and non-exposed to fetal growth restriction (FGR) newborns with the same date of birth. Children whose mother's name and medical code were registered in these records were selected for the study, regardless of their month of birth. FGR was defined as newborns weighing <10th percentile of the standard weight at birth [22].

The eligibility criteria were the absence of genetic syndromes, cardiovascular and/or endocrine diseases and to be healthy. Healthy subjects were understood to be participants without any medical conditions that act directly or indirectly to increase the cardiovascular risk. Large for gestational age newborns were excluded.

From the data recorded in the books of births, patients with a low birth weight (<2,500 g) and normal weight (between 2,500 and 3,999 g) were identified, to search for their records and analyze the neonatal data. The invitation to participate in this study was made through personal visits, phone calls and letters, using the contact data from the medical records. During the first conversation with the adult responsible for the adolescent, the study objectives were explained and a day was scheduled for the anthropometric and laboratory evaluations to be carried out.

Only 58 adolescents, aged between 10 and 20 years, with FGR, and 114 subjects with percentiles >10th for weight and gestational age at birth were assessed. The adolescents were of both gender and were born at the Assis Chateaubriand Maternity Teaching Hospital, one of the referral maternity hospitals for high-risk pregnancies in a urban population from Ceará state, Brazil, according to ***Fig*.1**.

The initial examination included a medical and family history, clinical interviews, followed by a fasting biochemical assessment at the Pr Dr Eurico Litton Pinheiro de Freitas Laboratory of Clinical and Toxicological Analysis, Federal University of Ceará (FUC - LCTA). Venous blood samples (10 mL) were collected between 08:00 and 09:00 at the FUC-LCTA, by puncturing a vein in the forearm after fasting for 12 hours. Vacutainer tubes containing separator gel were used to obtain the serum. The samples were analyzed by enzymatic colorimetric methods for glucose, total cholesterol, High Density Lipoprotein Cholesterol (HDL-c) and triglycerides and read on a semi-automated (Labtest Diagnostic S/A Lagoa Santa, MG, Brazil) system, following the manufacturer's guidelines. The Friedewald formula was used to determine the LDL-C (Low Density Lipoprotein Cholesterol) when triglycerides <400mg/dL [26]. The references of the I Guideline for Prevention of Atherosclerosis in Childhood and Adolescence [27] were adopted as normal parameters.

Height was measured using a 206 model Seca stadiometer attached to a wall. To check weight and the

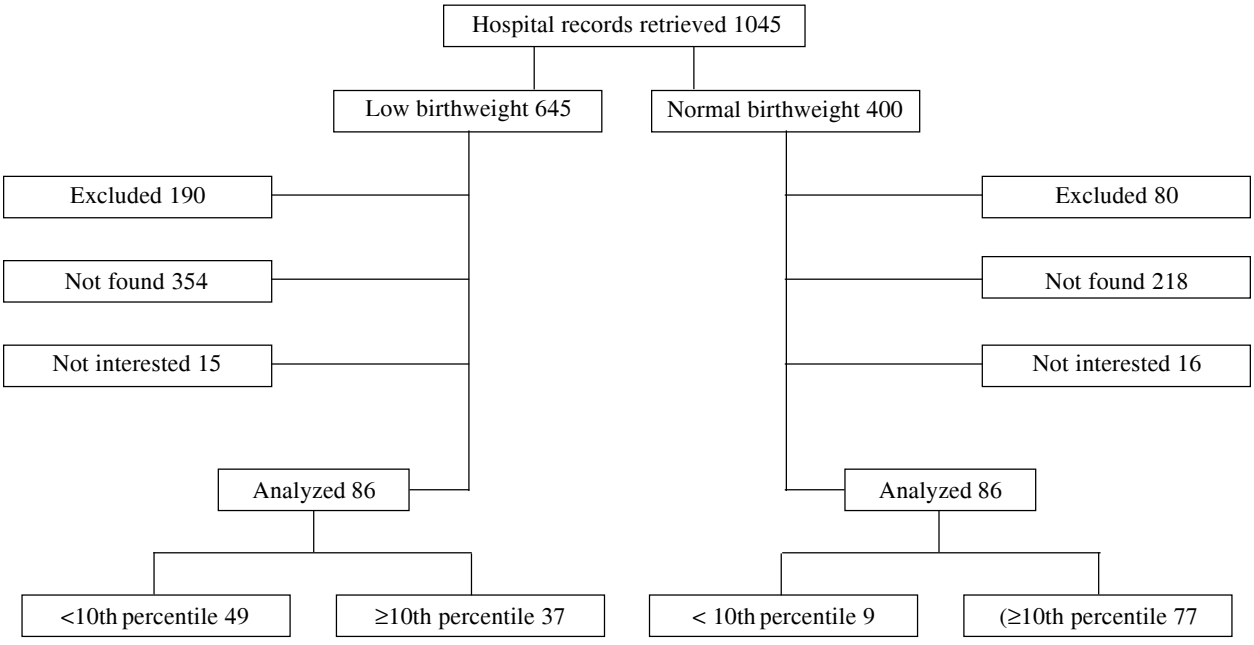

FIG. 1 *Study flow diagram.*

total percentage of body fat an Ultra SlimW835, Wiso digital analyzer was used. During the assessments the participants were standing without shoes wearing light clothing. The Body Mass Index (BMI) was calculated by dividing weight by height squared (in kilograms per square meter) and classified according to the WHO curves [23]. The circumference of the waist, abdomen and hips were measured using an anthro-pometric tape measure Model T872-Wiso at the end of a gentle expiration, taking as the reference point halfway between the lower rib and the top of the iliac crest and umbilical scar and the largest point of the outer hip, respectively. Moreover, the biceps fold of the right arm was measured using a skinfold caliper model Innovare 2 Cescorf.

Systolic and diastolic blood pressure were measured using a calibrated semi-automatic sphygmomanometer Microlife BP 3BTO-H model, after 30 minutes of rest. Two measurements were taken at 1 minute intervals and the average value was used for analysis. In case of a difference of ≥20 mmHg between the measurements, a new measurement was performed and the average of the two closest measurements was used as the final result for analysis.

Flow-mediated brachial artery dilatation (FMD): The examinations took place between 10:30 and 12:30, in a room with dimmed lighting and a controlled temperature (21 ºC to 24 ºC). We used a linear probe of a Sonoace X8, Medison device with a frequency of 6-9 MHz, positioned on the medial side of the abducted right arm, longitudinal and perpendicular to the skin, 5 cm above the antecubital crease. The brachial artery was insonated directly below biceps and beside the brachial muscle. The methodology developed by Cunha Filho, *et al*. [24] was followed in order to verify the luminal diameter of the brachial artery. Dilation was considered normal when ≥10% [25].

Statistical analyses: The sample size was calculated considering an alpha error of 5% and a confidence level of 80% (beta error of 20%) and, based on the occurrence of previous studies with relative risk for complications in the long term of approximately 2.3, an "n" of 160 patients was found. The Shapiro-Wilk test was used to test the normality of the continuous variables. The Student *t*-test, Kruskall Wallis test and Mann-Whitney test were used according to the normality of the continuous variables and Chi-square test for categorical variables. The level of significance was set at $P<0.05$. The STATA program version 12.0 was used for the statistical analysis.

RESULTS

***Web Table* I** shows the baseline data of the mothers of the participants, demonstrating no differences between the groups. ***Table* I** compares the perinatal data between the two groups. Neonatal outcomes were less favorable in the group with FGR: prematurity in more than 50% ($P=0.01$), 80% with a birth weight less than 2,500 g ($P<0.001$), and shorter height and smaller head and thoracic circumference ($P<0.001$).

Clinical and anthropometric data of the adolescents was similar in the two groups except for higher hip-circumference and higher total cholesterol levels in those without FGR ($P=0.04$ for both) (***Table* II**). No differences were noted between the groups with regards to the brachial artery measurements (***Table* III**).

DISCUSSION

The results only revealed a few anthropometric, metabolic, and endothelial differences associated with fetal growth restriction, specifically, hip circumference and total cholesterol, both with lower values in FGR ($P=0.04$ for both). In general, those exposed to FGR seem to be thinner and shorter, which affects other measurements such as waist and abdominal circumference, as well as the percentage of total fat, but without statistical differences.

This study has some limitations. The records of neonatal and maternal data were obtained at delivery for purposes of care and not to conduct research, leading to a lack of annotation of some parameters. In addition, possible errors filling in the registration can no longer be

TABLE I PERINATAL DATA IN THE STUDY POPULATION

Neonatal Characteristics	*Not FGR (n=114)*	*FGR (n=56)*
Male	43 (37.7)	22 (37.9)
Preterm (<37 wks)[$]	37 (32.5)	30 (51.7)
*Weight (Kg)[#]	2.81 (0.8)	1.94 (0.49)
VLBW (<1.5 Kg)[#]	6 (7.1)	12 (20.7)
LBW (<2.5 Kg)	30 (26.3)	37 (63.8)
Underweight (2.5-2.9 Kg)	15 (13.2)	9 (15.5)
Appropriate weight (3.0-3.9 Kg)	62 (54.4)	0
*Length (m)[#]	0.47 (0.4)	0.43 (0.34)
Ponderal index[#]		
<2.25	15 (13.3)	21 (36.2)
> 2.25	98 (86.8)	37 (63.8)
*Head circumference (cm)[#]	32.9 (3.5)	31.0 (2.3)
*Chest circumference (cm)[#]	32.1 (3.8)	28.2 (3.3)
Complications at birth	71 (62.8)	42 (72.4)

*Value in n (%) or *Mean (Standard Deviation); VLBW: very low birth weight; LBW: low birth weight; FGR: Fetal growth retardation [#] P<0.001; [$] P=0.01.*

TABLE II CLINICAL AND METABOLIC DATA IN ADOLESCENTS ACCORDING TO FETAL GROWTH RESTRICTION

Characteristics	*Not FGR*	*FGR*	*P*
Anthropometric variables			
Age (y)	13.4 (2.8)	12.9 (2.4)	0.35
Weight (Kg)	51.3 (14.6)	46.9 (11.3)	0.06
Height (m)	1.55 (0.1)	1.52 (0.1)	0.12
BMI (kg / m^2)	21.3 (5.0)	20.1 (3.8)	0.20
SBP (mmHg)	101.8 (12.6)	101.9 (11.4)	0.98
DBP (mmHg)	64.6 (8.3)	63.6 (8.1)	0.45
AC (cm)	75.8 (12.6)	72.3 (10.3)	0.12
WA (cm)	70.0 (11.9)	66.9 (8.1)	0.16
HC (cm)	89.1 (11.8)	85.4 (9.9)	0.04
WHR	0.8 (0.1)	0.8 (0.1)	0.71
WHtR	0.6 (0.1)	0.5 (0.1)	0.45
Biceps fold (mm)	8.0 (4.3)	7.6 (4.0)	0.56
Body fat (%)	28.0 (9.3)	26.5 (9.7)	0.32
Metabolic variables			
Total cholesterol (mg/dL)	146.4 (26.0)	136.9 (22.5)	0.04
Triglycerides (mg/dL)	73.5 (38.4)	68.7 (26.1)	0.93
HDL-c (mg/dL)	44.2 (10.4)	43.2 (9.7)	0.60
LDL-c (mg/dL)	86.6 (23.3)	79.9 (19.7)	0.17
VLDL-c (mg/dL)	14.6 (7.5)	13.7 (5.2)	0.93
Fasting glucose (mg/dL)	81.3 (9.1)	79.5 (13.3)	0.64

BMI: Body Mass Index, SBP: systolic blood pressure, DBP: diastolic blood pressure, AC: Abdominal circumference, WC: waist circumference; HC: hip circumference, WHR: waist to hip ratio; WHtR: waist height ratio, LDL-C: Low-Density; Lipoprotein; HDL-C: High-Density Lipoprotein Cholesterol; VLDL-c: Very-Low Density Lipoprotein Cholesterol.

TABLE IIII BRACHIAL ARTERY MEASUREMENTS IN ADOLESCENTS ACCORDING TO BIRTHWEIGHT

Characteristics	*Not FGR*	*FGR*	*P*
*Basal diameter (mm)	2.56 (0.31)	2.58 (0.34)	0.81
*Post-occlusion diameter (mm)	2.86 (0.35)	2.92 (0.37)	0.42
*FMD, (%)	11.96 (6.24)	13.43 (6.41)	0.13
Endothelial dysfunction <10%, *n*(%)	41 (36)	15 (26)	0.18

*FMD, flow-mediated dilatation of the brachial artery; *Mean (SD).*

confirmed or corrected, due to the time elapsed. As no previous measurements of the parameters analyzed in this study had been performed, it was not possible either to identify whether there had been rapid growth during childhood or to verify if it would have a more significant effect than FGR, as found in some studies. Nor was it possible to carry out the analysis excluding premature subjects in both groups, as this would cause the loss of more than half the patients in the group with FGR. In addition, prior to 1998, many records were destroyed due to inadequate care, so the number of participants over 15 years old was reduced. To reduce bias, we controlled for the socioeconomic status. Furthermore, we have not investigated the effects of rapid growth in children with FGR. An important feature in this study is that socioeconomic status and the same day of birth was accounted for and the groups were similar in maternal and family characteristics, mean chronological age and gender. Medical registers were used to investigate weight and height at birth in order to minimize wrong values. We used international parameters to facilitate future comparisons with our data.

Monteiro, *et al.* [9], in a cohort study in Southern Brazil, with adolescents aged 14 to 16 years found no association between FGR and overweight/obesity among girls, whereas for boys, the association was positive for both conditions. Another study, which gathered data from five countries: India, Guatemala, the Philippines and Brazil showed that the greatest above normal weight gain at any age was related to elevated blood pressure in young adults, who had their weight monitored after birth, at 12, 24 and at 48 months, with the latest measurements taken on average at age 23. However, faster weight gain in infancy did not represent a greater risk than weight gain at other ages [30]. Some authors argue that it is not fetal restriction or low birth weight that impact negatively on cardiovascular health, but instead greater than expected growth, either in weight or height, also known as catch-up growth. Furthermore, the effect of accelerated growth itself after birth is controversial. In lower income countries, its occurrence appears to reduce the morbidity and mortality of children with FGR [28]; a fact not observed in countries with high incomes, where it appears to be associated with an increased prevalence of cardiovascular disease [21]. It is possible that other measurements besides birth weight may be more strongly associated with adverse cardiovascular outcomes than birth weight alone [28].

These results do not exclude the possibility of an association between accelerated growth during the first years of life in those with FGR and worsening risk factors. It is suggested that prospective longitudinal studies with multiple assessments throughout the study period are performed to verify the effect of accelerated growth in similar populations.

Contributors: All authors have planned, executed, construction of the research, implemented of survey, analysis and interpretation of data and approved the final version of the manuscript.

WHAT IS ALREADY KNOWN?

- Fetal growth restriction is associated with some cardiovascular risk factors such as blood pressure, increased anthropometric measurements, endothelial dysfunction and metabolic syndrome at later ages.

WHAT THIS STUDY ADDS?

- Only lower hip circumference and total cholesterol in adolescence were found to be associated with fetal growth restriction.

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Competing interests: None stated.

REFERENCES

1. Lee ACC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al*. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health. 2013;1:e26-e36.
2. WHO ECoPS. Physical status: The use of and interpretation of anthropometry, Report of a WHO Expert Committee. 1995. Geneva: World Health Organization.
3. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, *et al*. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 2008;371:243-60.
4. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, *et al*. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008;371:340-57.
5. Barker DJP. Fetal origins of coronary heart disease. BMJ. 1995;311:171-4.
6. Barker DJP, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki Birth Cohort. Ann Hum Biol. 2009;36:445-58.
7. Cheung YF, Wong KY, Lam BCC, Tsoi NS. Relation of arterial stiffness with gestational age and birth weight. Arch Dis Child. 2004;89:217-21.
8. Jafar T, Qadri Z, Islam M, Hatcher J, Bhutta Z, Chaturvedi N. Rise in childhood obesity with persistently high rates of undernutrition among urban school-aged Indo-Asian children. Arch Dis Child. 2008;93:373-8.
9. Monteiro POA, Victora CG, Barros FC, Monteiro L. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. Int J Obes. 2003;27:1274-82.
10. Dotsch J. Renal and extrarenal mechanisms of perinatal programming after intrauterine growth restriction. Hypertens Res. 2009;32:238-41.
11. Zanardo V, Fanelli T, Weiner G, Fanos V, Zaninotto M, Visentin S, *et al*. Intrauterine growth restriction is associated with persistent aortic wall thickening and glomerular proteinuria during infancy. Kidney Int. 2011;80:119-23.
12. Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. J Physiol. 2006;572:31-44.
13. Leeson CPM, Whincup PH, Cook DG, Donald AE, Papacosta O, Lucas A, *et al*. Flow-mediated dilation in 9- to 11-year-old children: The influence of intrauterine and childhood factors. Circulation. 1997;96:2233-8.
14. Belfort MB, Rifas-Shiman SL, Rich-Edwards J, Kleinman KP, Gillman MW. Size at birth, infant growth, and blood pressure at three years of age. J Pediatr 2007;151:670-4.
15. Donker GA, Labarthe DR, Hamst RB, Selwyn BJ, Srinivasan SR, Wattigney W, *et al*. Low birth weight and serum lipid concentrations at age 7–11 years in a biracial sample. Am J Epidemiol. 1997;145:398-407.
16. Rodríguez-Soriano J, Aguirre M, Oliveros R, Vallo A. Long-term renal follow-up of extremely low birth weight infants. Pediatr Nephrol. 2005;20:579-84.
17. Fattal-Valevski A, Bassan H, Bernheim J, Redianu B, Leitner Y, Harel S. Blood pressure values in 8-12 year old children with a history of intrauterine growth retardation. Isr Med Assoc J. 2011;13:480-4.
18. Rossi P, Tauzin L, Marchand E, Boussuges A, Gaudart J, Frances Y. Respective roles of preterm birth and fetal growth restriction in blood pressure and arterial stiffness in adolescence. J Adolesc Health. 2011;48:520-2.
19. Vielwerth SE, Jensen RB, Larsen T, Holst KK, Mølgaard C, Greisen G, *et al*. The effect of birthweight upon insulin resistance and associated cardiovascular risk factors in adolescence is not explained by fetal growth velocity in the third trimester as measured by repeated ultrasound fetometry. Diabetologia. 2008 51:1483-92.
20. Victora CG, Barros FC, Horta BL, Martorell R. Short-term benefits of catch-up growth for small-for-gestational-age infants. Int J Epidemiol. 2001;30:1325-30.
21. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001;322:949-53.
22. Pedreira CE, Pinto FA, Pereira SP, Costa ES. Birth weight patterns by gestational age in Brazil. An Acad Bras Cienc. 2011;83:619-25.
23. Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85:660-7.

24. Cunha Filho EV, Mohr C, Acauan Filho BJ, Gadonski G, Paula LG, Antonello ICF, *et al*. Flow-mediated dilatation in the differential diagnosis of preeclampsia syndrome. Arq Bras Cardiol. 2010;94:182-6.
25. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, *et al*. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340:1111-5.
26. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.
27. Giuliano ICB, Caramelli B, Pellanda L, Duncan B, Mattos S, Fonseca FH. I diretriz de prevenção da aterosclerose na infância e na adolescência. Arq Bras Cardiol. 2005;85.
28. Lucas A, Fewtrell M, Cole T. Fetal origins of adult disease-the hypothesis revisited. BMJ. 1999;319:245.
29. Hemachandra AH, Howards PP, Furth SL, Klebanoff MA. Birth Weight, Postnatal growth, and risk for high blood pressure at 7 years of age: Results from the Collaborative Perinatal Project. Pediatrics. 2007;119:e1264-e70.
30. Adair LS, Martorell R, Stein AD, Hallal PC, Sachdev HS, Prabhakaran D, *et al*. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low-and middle-income-country cohorts: when does weight gain matter? Am J Clin Nutr. 2009;89:1383-92.