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Size at birth and lipoprotein concentrations in adulthood: two prospective studies in Latin American cities

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ABSTRACT

Background The relationship between birth weight and plasma lipoproteins is inconsistent.

Aims To assess the association between birth weight and (1) body mass index (BMI) at birth and (2) lipoproteins in young adults, and also to explore the possible effect of current obesity as a possible effect modifier.

Methods Two prospective studies based on representative samples of subjects born in the 1970s were carried out in Ribeirão Preto, Brazil (n=2063) and Limache, Chile (n=999). The surveys were carried out between 2001 and 2004.

Results Mean birth weights were 3267 g and 3177 g and mean adult BMIs were 24.3 kg/m^2 and 25.8 kg/m^2 in the Brazilian and Chilean samples, respectively. Total adult cholesterol was 4.57 mmol/l in Chileans, 0.26 mmol/l higher than in Brazilians ($p<0.001$). The main finding was an interaction between adult obesity (BMI 30 or over) and birth weight and also BMI at birth and low-density lipoprotein (LDL) and total cholesterol. A birth-weight increment of 1 kg was associated with a decrease in total cholesterol (−0.374 mmol/l, 95% CI −0.567 to −0.181) and LDL (−0.304 mmol/l (−0.479 to −0.129) in obese participants only. These associations persisted after allowing for gestational age in a smaller sample. This finding was consistent in separate analyses in the Brazilian and Chilean samples. No associations were found in relation to high-density lipoprotein and triglyceride concentrations.

Conclusion The results suggest that those who were of low birth weight and are obese are more likely to have high cholesterol and LDL concentrations. Thus preventing obesity may be especially rewarding in subjects with a low birth weight.

Although several reports support a relationship between birth weight and coronary heart disease, and also between birth weight and high blood pressure and diabetes mellitus,[1 2] the evidence for an association between impaired growth in utero, as assessed by birth weight, and adult lipoprotein concentrations in plasma remains elusive and far from compelling.[3–5] Although Huxley and colleagues[6] documented a negative association between birth weight and lipoprotein concentration in their meta-analysis, they also showed a large heterogeneity between studies, which led them to conclude that impaired fetal growth does not have an effect on blood cholesterol concentration that would have a material impact on risk of vascular disease.

Most of the available studies have been carried out in highly developed industrialised countries,[7 8] thus it would be relevant to assess the hypothesis in countries in which fast economic development, characterised by marked inequality in wealth distribution, has only just started, such as Brazil and Chile.[9] In these two countries, infant mortality and undernutrition were common features in the 1970s, but the situation has greatly improved in recent years.[10 11] Undernutrition in infancy has been replaced by obesity to levels similar to those reported in some developed countries,[12] especially in Chile.[13] These changes in health status provide a unique opportunity for assessing two avenues in relation to fetal growth and lipoprotein concentration that have not been previously explored: firstly, to assess whether size at birth is associated with lipoprotein concentration in countries that are experiencing a rapid change in nutritional status and an increase in chronic diseases such as cardiovascular diseases and cancer; secondly, to assess whether the relationship, if detected, is restricted only to one group in the community—for example, those who are obese. In such a context, size at birth on its own would be insufficient to influence lipoprotein concentration. Such effect modification has been previously shown in relation to coronary heart disease restricted to those with a degree of obesity.[14]

The opportunity arose to assess the possible impact of birth weight on lipoprotein concentrations using information from two prospective studies carried out in two Latin-American countries, both of which are experiencing rapid changes in disease pattern towards an increase in the prevalence of chronic diseases. The aim of this study was to assess the association between size at birth and lipoprotein concentration in young adults from Ribeirão Preto in Brazil and Limache in Chile. Our analysis was based on longitudinal studies which used broadly the same methodology, collected similar information at birth, and whose participants were reassessed in the third decade of life. An advantage of our study was the ability to assess the consistency of findings in these two settings.

METHODS

The sample

A concurrent longitudinal design was used in the Brazilian study and a non-concurrent longitudinal design in the Chilean study. Although the Chilean study was conceived in 2001, the existence of

a birth register with anthropometric measurements based on standardised norms was available for analysis. Indeed the selection of subjects was based on the birth register.

The Brazilian study was carried out between 2002 and 2004 in 2063 adults selected from a sample of 5665 singletons born between 1 June 1978 and 31 May 1979 who were alive at the age of 20 years in Ribeirão Preto. The sample was stratified by three social strata levels based on neighbourhood. Further details of this cohort can be found elsewhere.[15] Ribeirão Preto is a city of half a million inhabitants located in the southeast region of Brazil, State of Sao Paulo. The economic wealth of this city is related to the sugar cane agro-industry, commerce and services, and it has one of the most important universities in the country.

The Chilean study was carried out between 2001 and 2003. It included 999 subjects aged 22–28 years who were randomly selected from a sampling frame of 3096 newborns registered between 1 January 1974 and 31 December 1978 in the maternity hospital of Limache.[16] Limache is a small agricultural area 120 km from Santiago, the capital city.

A proportion of the Brazilian sample (12.8%) and the Chilean sample (21%) did not participate because of unwillingness to take part in the study, emigration, death, a custodial sentence or a mental disability. They were randomly replaced using the same sampling frame. The levels of migration in Limache and Ribeirão-Preto are low because of the low unemployment rates in these two settings. The two samples can be considered representative of the areas selected, but not of Brazil and Chile as a whole.

Information

The same questionnaire was used in the two studies to collect socioeconomic and demographic data on the families and smoking status. The anthropometric measurements were carried out at hospitals, and the blood samples were obtained after a fasting period of 12 h. In both countries, written and verbal instructions were given by university nurses in a face-to-face conversation, and reinforced later by telephone calls. The test was repeated in those whose lipoprotein concentrations appeared to be too high or too low.

The anthropometric measurements, in both countries, were made by trained university nurses following international standards.[17] Height was measured in barefoot subjects to the last complete millimetre, and weight was measured using periodically calibrated beam weighing scales, with subjects wearing light clothes. Final weight was obtained adjusted for clothes worn.

In both countries, total cholesterol and triglycerides were measured using a colorimetry enzymatic method.[18] In Chile, the reagents were provided by Gesellschaft fur Biochemica and Diagnostica and in Brazil by Dade Behring Dimension. High-density lipoprotein (HDL) was measured by precipitation by the technique of Seigler and Wü,[19] and low-density lipoprotein (LDL) concentrations were estimated using Friedewald's formula.[20]

In Chile, weight and length at birth were obtained from records in the maternity ward. These measurements were carried out by midwives following the established norms released by the national health services, which have remained unchanged.[21] In Brazil, weight and length at birth were measured by trained nurses. In both settings, the newborns were weighed, without clothes, immediately after birth using scales calibrated periodically to an accuracy of 10 g. Length was measured using a tape measure, with the child lying in a supine position.

The main analysis was based on multiple regression models in which the dependent variables were total cholesterol, LDL, HDL and triglyceride concentrations, and the independent variables were birth weight or body mass index (BMI) at birth, birth weight adjusted for gestational age using the Canadian reference,[22] and obesity in adulthood. All analyses were adjusted for sex, age, country, current smoking and years of full-time schooling as possible confounders. With the exception of country, all these variables have often been included in previous analyses as possible confounders.[4] Effect modifications between the anthropometric measures at birth and obesity (BMI of 30 kg/m^2 or over) in adulthood on each of the outcomes in the analysis were estimated. We also assessed possible interactions between anthropometric measurements at birth and sex on lipid concentrations.

The studies were approved by the ethics committees of the Faculty of Medicine of the University of Chile and the Faculty of Medicine of the University of Sao Paulo in Riberão Preto. The participants were asked to sign a consent form after reading, or listening to, explanatory notes about the research.

RESULTS

The Brazilian sample had a higher percentage of subjects with a full time education of 12 years or more than the Chilean sample, 34.1% and 21.7%, respectively ($p<0.001$). No differences between sexes were observed (data not shown).

Birth weight was higher in the Brazilian sample than in the Chilean sample ($p<0.001$), but length at birth was greater in Chileans than in Brazilians ($p<0.001$) (table 1). Thus the BMI at birth of Brazilians was greater than that of Chileans ($p<0.001$).

Mean BMI and prevalence of obesity in adulthood were markedly higher in the Chilean sample than in the Brazilian sample ($p=0.001$ and $p=0.006$ respectively) (table 1). After stratification by sex, differences in BMI and obesity in adulthood were restricted to women only (table 1). For measurements at birth, the pattern for the whole group and after stratification by sex was similar, except that the difference in length was restricted to women only.

Total cholesterol, LDL and triglyceride concentrations were higher in the Chilean than the Brazilian sample ($p<0.001$), but HDL concentration was higher in the Brazilian than the Chilean sample ($p<0.001$). Thus there was a more unfavourable lipoprotein profile in the Chilean sample (table 2). The differences between countries were consistent in the two sexes (table 2).

As we found a consistent interaction between BMI in adulthood and birth weight, birth weight adjusted for gestational age and BMI at birth on total cholesterol and LDL ($p<0.001$), we present results stratified by obesity status in adulthood (table 3). Birth weight, adjusted and unadjusted for gestational age, and BMI at birth were negatively associated with total cholesterol and LDL, but only in those who were obese. Adult total cholesterol decreased by −0.37 mmol/l for each kg of increment in birth weight, −0.19 mmol/l for each z-score of birth weight adjusted by gestational age, and −0.13 mmol/l for each unit of BMI (kg/m^2) at birth. A similar decrease was observed for LDL. In contrast, birth weight (adjusted or unadjusted for gestational age) and BMI at birth were consistently not associated with HDL and triglyceride concentrations regardless of obesity status (table 3). The significant negative associations for total cholesterol and LDL were confirmed for the Brazilian and Chilean samples in analyses stratified by country (p values from 0.03 to 0.002). We did not find any associations in the non-obese groups regardless of outcome (table 3). Birth weight (adjusted or

Table 1 Anthropometric measurements (means and 95% CI) at birth in Chilean and Brazilian young adults by sex

Variable	Chile (n=999)			Brazil (n=2063)			Chile versus Brazil (women; p value	Chile versus Brazil (men; p value
	Men	Women	Total	Men	Women	Total		
Birth weight (g)	3204 (3156 to 3252)	3157 (3113 to 3202)	3177 (3150 to 3212)	3338 (3306 to 3370)	3203 (3173 to 3233)	3267 (3246 to 3289)	0.088	0.001
BMI at birth (kg/m^2)	12.95 (12.81 to 13.10)	12.97 (12.83 to 13.10)	12.96 (12.86 to 13.05)	13.55 (13.46 to 13.65)	13.39 (13.30 to 13.48)	13.46 (13.40 to 13.52)	0.001	0.001
Length at birth (cm)	49.64 (49.45 to 49.83)	49.29 (49.10 to 49.48)	49.44 (49.31 to 49.57)	49.53 (49.39 to 49.67)	48.81 (48.68 to 48.95)	49.16 (49.06 to 49.26)	0.001	0.396
Adult BMI (kg/m^2)	25.36 (25.01 to 25.72)	26.19 (25.77 to 26.62)	25.82 (25.54 to 26.09)	25.02 (24.73 to 25.30)	23.66 (23.34 to 23.97)	24.29 (24.08 to 24.50)	0.001	0.167
Obesity in adult life (%)	10.22 (7.27 to 13.16)	19.54 (16.14 to 22.94)	15.48 (13.2 to 17.7)	12.58 (10.44 to 14.71)	11.04 (9.09 to 12.99)	11.8 (10.4 to 13.2)	0.001	0.213

BMI, body mass index.

unadjusted for gestational age) explained approximately 1% of the variation in total cholesterol and LDL in the obese group and almost 0% in the non-obese group.

DISCUSSION

The main finding of the study was a consistent interaction between birth weight and BMI at birth and obesity in adulthood on LDL and total cholesterol. The interaction persisted when birth weight was adjusted for gestational age in a smaller sample of participants. These findings were observed separately in the Brazilian and the Chilean sample. Birth weight and BMI at birth were not associated with HDL and triglycerides.

Interpretation of the results

Published meta-analyses have reported a weak negative association between birth weight and total cholesterol in both sexes in adolescent as well as adult populations.[3 6] The evidence of an association between birth weight and LDL is inconsistent, although it has been found in children and adults of both sexes.[3 5] Likewise the association of birth weight with HDL has been inconsistent, as both positive and negative associations have been reported.[5 23] Consistent association was found in the literature between birth weight and triglyceride concentrations.[3 23–27]

Our findings would suggest that a lower birth weight would make a subject more susceptible to having an unfavourable lipid profile if he/she were to become obese in adulthood. This finding is relevant for public health because it would indicate that obesity prevention would reduce the risk of a high LDL concentration or total cholesterol in the population. Although the association is consistent in Brazil and Chile, it explains only 1% of the variation. Our study does not offer an explanation for our finding, although it has been suggested that, in low-birth-weight babies, an alteration in lipid metabolism may originate in fetal life. It has been suggested that, in an adverse intrauterine environment during fetal development, there are changes in the distribution of the blood flow, prioritising brain perfusion to the detriment of visceral flow. Such a distorted flow could alter liver function.[28] Our findings indicate that impaired fetal growth would increase the susceptibility of high lipoprotein concentrations, but only in those who are obese in adulthood.

The interaction between obesity in the adult and birth weight and BMI at birth emphasises the importance of nutritional status in adults, especially excessive weight gain. It has been hypothesised that food restriction in early life may lead to an efficient use of energy and the so-called thrifty phenotype. If individuals with this phenotype do not experience any energy restriction later in life, they will keep using energy efficiently and accumulate more weight than those without this phenotype.[29] This hypothesis has found some support from follow-up studies of children in whom fast weight gain after birth was reported to have a greater unfavourable effect on concentrations of blood lipoproteins.[30]

In Chile and Brazil, since the 1970s, babies with low birth weight as well as underweight children have been clinically managed with a high-energy diet to facilitate catch-up growth in the shortest possible time. It is well known that early energy restrictions followed by increased weight in adult life is a predominant feature in places that have had a fast nutritional transition, such as Chile and Brazil, where a high prevalence of low birth weight in the past and excess weight in adult life are common.[13 31]

Our findings support the view that fetal programming as well as environmental conditions are responsible for the increase in high concentrations of total cholesterol and LDL, although not of HDL and triglyceride concentrations. As these associations were detected in young adult populations, it is possible that amplification may occur over time, as suggested for high blood pressure.[39]

Obesity control in populations exposed to fetal malnutrition, a common situation in some developing countries, may offer a feasible intervention to lower total cholesterol and LDL. However, it would be impractical to tailor an intervention to only those who had low birth weight regardless of obesity

Table 2 Plasma lipid concentrations (means and 95% CI) according to sex and country in Chilean and Brazilian young adults

	Chile			Brazil			Chile versus Brazil (men; p value)	Chile versus Brazil (women; p value)
	Men (n=437)	Women (n=562)	Total (N=999)	Men (n=987)	Women (n=1050)	Total (N=2037)		
Total cholesterol (mmol/l)	4.51 (4.42 to 4.60)	4.62 (4.53 to 4.70)	4.57 (4.51 to 4.63)	4.25 (4.19 to 4.31)	4.36 (4.31 to 4.42)	4.31 (4.27 to 4.35)	0.001	0.001
LDL (mmol/l)	2.85 (2.77 to 2.93)	3.00 (2.92 to 3.08)	2.94 (2.88 to 2.99)	2.60 (2.55 to 2.65)	2.56 (2.52 to 2.61)	2.58 (2.55 to 2.62)	0.001	0.001
HDL (mmol/l)	1.01 (0.99 to 1.04)	1.1 (1.07 to 1.12)	1.06 (1.04 to 1.08)	1.12 (1.10 to 1.14)	1.35 (1.33 to 1.37)	1.24 (1.22 to 1.25)	0.001	0.001
Triglycerides (mmol/l)	1.41 (1.33 to 1.50)	1.15 (1.10 to 1.20)	1.26 (1.22 to 1.31)	1.18 (1.11 to 1.25)	0.99 (0.96 to 1.02)	1.08 (1.05 to 1.12)	0.001	0.001

Table 3 Association between anthropometric measurements at birth by adult obesity status and plasma concentrations of total cholesterol, LDL, HDL and triglycerides

	Total cholesterol (mmol/l)			LDL (mmol/l)			HDL (mmol/l)			Triglycerides (mmol/l)		
	Coef	95% CI	p Value	Coef	95% CI	p Value	Coef	95% CI	p Value	Coef	95% CI	p Value
Birth weight (kg)												
Obese (n=392)	−0.374	−0.567 to −0.181	0.001	−0.304	−0.479 to −0.129	0.001	0.003	−0.051 to 0.058	0.900	−0.149	−0.421 to 0.122	0.280
Non-obese (n= 2632)	−0.008	−0.079 to 0.064	0.830	0.014	−0.049 to 0.077	0.671	−0.008	−0.032 to 0.015	0.500	−0.018	−0.068 to 0.032	0.476
BMI at birth (kg/m^2)												
Obese (n=392)	−0.131	−0.195 to −0.066	0.001	−0.109	−0.167 to −0.051	0.001	0.001	−0.017 to 0.020	0.878	−0.042	−0.133 to 0.049	0.361
Non-obese (n= 2618)	−0.008	−0.032 to 0.016	0.525	−0.003	−0.024 to 0.019	0.807	−0.000	−0.008 to 0.007	0.926	−0.005	−0.022 to 0.012	0.565
Birth weight adjusted by gestational age (z-score)												
Obese (n=336)	−0.187	−0.286 to −0.089	0.001	−0.141	−0.023 to −0.054	0.002	−0.010	−0.038 to 0.018	0.497	−0.088	−0.235 to 0.060	0.244
Non-obese (n=2376)	−0.013	−0.046 to 0.021	0.456	−0.007	−0.037 to 0.023	0.640	−0.003	−0.014 to 0.008	0.592	−0.002	−0.026 to 0.022	0.891

Adjusted for age, sex, country, current smoking and years of full-time education.
BMI, body mass index; Coef, coefficient on the lineal regression; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

status. If anything, the more appropriate approach may be to provide extra resources for tackling obesity to those who had low birth weight. It is important to remember that we used birth weight as a continuous variable in our analysis, and we found a linear negative association with total cholesterol and LDL. Thus we use low birth weight as a relative term not following the usual definition of newborns who are less than 2500 g.

Strengths and weakness

The strengths of our analysis are the availability of two prospective studies representative of the two communities, with a very high response rate in which we used broadly the same methodology and the subjects were of similar age. The measurements were taken by trained personnel. A possible weakness is that the reagents used in the two studies to assess lipoproteins came from different companies. However, we adjusted for country, both laboratories were following international standardised protocols, and quality control arrangements were in place. Furthermore, our main findings were replicated to a great extent in the two countries in separate analyses. Another possible disadvantage is that the two cities in this study are dissimilar. Ribeirão Preto is an urban area and the wealthiest city in Brazil, whereas Limache is an agricultural area, which has a narrow socioeconomic stratification in comparison with Ribeirão Preto. However, the fact that the results were consistent in the two locations despite the socioeconomic differences enhances the value of our findings. A methodological issue is that current obesity and lipid concentrations were assessed at the same time. Thus we have to be cautious in the interpretation of our finding that obesity modifies the effect of the association between anthropometric measurements at birth and lipid concentrations. However, it is unlikely that lipid concentrations influence obesity. We acknowledge that emigration is not a random phenomenon and that may have rendered the analysed samples less representative. We believe that, of the main variables in our analysis, only obesity might be associated with emigration, but we do not know of any study that has demonstrated emigration by obesity status. However, even if obesity were to cause such a distortion, the regressions in our study were stratified by obesity status, thus bias would be unlikely to explain our results. Finally, as in any prospective analysis, residual confounding may have explained the associations shown in our study—for example, if years of full-time education were a poor proxy measure of socioeconomic level. We carried out further analysis, but only in the Chilean sample, adding number of household belongings from zero to five (microwave, refrigerator, washing machine, car and gas-fuelled heating devise) as a measure of socioeconomic status. The significant associations hardly changed after adding household belongings to the analyses.

If our results were replicated in other studies, our findings would greatly increase our knowledge about a mechanism to explain increases in LDL and total cholesterol in the population. It would also provide further ammunition for directing interventions to prevent obesity, with an emphasis on those who had lower birth weight within a community.

What is already known on this subject

- Several studies have reported a relationship between birth size and coronary heart disease including high blood pressure and diabetes mellitus.
- Evidence for an association between impaired growth in uterus and plasma lipoprotein concentrations in adults remains controversial.

What this study adds

- This study has shown an inverse association between birth size and total cholesterol including low density lipoproteins in those who were obese in adulthood, but not in those who were not.
- This finding was consistent for the Brazilian and the Chilean samples.

Policy implications

If the finding of this study were replicated, it would reinforce the view that a life course approach could be a helpful tool to prevent coronary heart disease because a low size at birth and obesity in adulthood would greatly increase the risk of coronary heart disease compared with low size at birth and obesity separately.

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Competing interests None.

Patient consent Obtained.

Ethics approval The studies were approved by the ethics committees of the Faculty of Medicine of the University of Chile and the Faculty of Medicine of the University of Sao Paulo in Ribeirão Preto.

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