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Short-term benefits of catch-up growth for small-for-gestational-age infants

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Background	Recent studies suggest that small newborns who present rapid postnatal growth may have an increased risk of chronic diseases in adulthood. On the other hand, it is widely assumed that catch-up growth is desirable for low birthweight children, but the literature on this subject is limited.
Methods	Population-based cohort study in southern Brazil, with 3582 children examined at birth, 20 and 42 months of age. Catch-up growth from 0 to 20 months was related to subsequent risks of hospital admissions and mortality.
Results	Children who were small-for-gestational-age (SGA) but presented substantial weight gain (≥0.66 z-score) up to the age of 20 months had 65% fewer subsequent hospital admissions than other SGA children (5.6% versus 16.0%; $P < 0.001$). Mortality to age 5 years was 75% lower (3 versus 13 per 1000, a non-significant difference based on a small number of deaths) for rapid-growing SGA children compared to the remaining SGA children. Their admission and mortality rates were similar to those observed for children born with an appropriate birthweight for their gestational age (AGA). Similar positive effects of rapid growth were found for AGA children.
Conclusion	There appear to be definite benefits associated with catch-up growth. Growth promotion efforts for infants who are born small should take into account their possible short- and long-term consequences.

Keywords	Growth, cohort study, infant, small for gestational age, mortality, hospitalization
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Recent research on the long-term consequences of fetal and early postnatal growth suggests that rapid growth in childhood may have detrimental consequences on adult health.

In 1995, English researchers[1] suggested that fast growth in the first year of life was associated with lower coronary morbidity in adults. However, at least four subsequent studies showed opposite associations. In a cohort study from Finland, there was increased coronary mortality for adult men who were thin at birth but whose weight caught up in childhood;[2] for women, catching up in height rather than weight was associated with higher coronary morbidity and mortality.[3] Still in Finland, subjects who were in a higher quartile of body mass index at 7 years of age than their birthweight quartile had a non-significantly increased risk (odds ratio = 2.3; 95% CI : 0.9–5.4) of metabolic syndrome as adults.[4] These findings suggest that there seems to be an interaction between size at birth and childhood growth in causing chronic diseases. English infants who gained more than 0.67 z-score of weight or length for age between birth and 2 years were fatter and had more central fat distribution at the age of 5.[5]

These findings on the negative effects of fast childhood growth are consistent with the results of studies on growth from birth to adulthood. In Wales, coronary heart disease incidence was highest for subjects whose birthweight was in the lowest tertile and their adult body mass index in the highest tertile.[6] In Sweden, blood pressure was increased for men who were light at birth (<3250 g) but whose adult height was above the median.[7]

Many authors have studied the long-term consequences of low birthweight on chronic diseases. However, as Lucas *et al.*[8] stressed, this association often became apparent only when adult body size was adjusted for. Mathematically, this suggests that change in body size—and not small size at birth *per se*—was the factor associated with chronic disease. This finding is also consistent with the studies reporting a negative effect of catch-up, as described above.[9]

As long ago as 1950, it was suspected that rapid growth among children who were stunted in early life could be detrimental.[10]

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Research from Brazil, China, Russia and South Africa suggests that stunted children have a 2–8 times greater risk of becoming overweight, a major concern given the rising importance of preventing obesity in childhood.[11] While stunted children from Guatemala tend to have lower per cent body fat as adults, they are at increased risk of central fatness.[12]

While most of the studies reviewed above cannot separate early catch-up (fast growth in infancy among small newborns) from late catch-up (weight gain for children who faced malnutrition in the first couple of years of life), several of them suggest that children who are small at birth and then catch up seem to be at a particularly high risk. A recent publication from Finland has separated the effects of rapid growth in infancy and from 1 to 12 years.[13] Irrespective of size at birth, rapid weight gain in infancy reduced the risk of coronary heart disease in adulthood. After 12 months, rapid growth increased this risk, but only in children who were thin at birth.

These recent results are particularly worrisome for Public Health practitioners, particularly in developing countries, who are actively involved in promoting catch-up growth in infancy and beyond. In these countries it is estimated that 25% of all newborns are growth-retarded.[14] Through growth monitoring programmes, counselling is provided to mothers whose children present low weight for age, or who are not putting on weight as expected.[15,16] This includes increasing meal frequency and—for children who are no longer exclusively breastfed—providing additional energy-dense and micronutrient-rich foods to promote fast growth.[17] Success is assessed through weight gain, since measuring child length in first-level health facilities is problematic. If effective, growth monitoring programmes will lead both to early and to late catch-up since they provide feeding advice to all malnourished children under 5 years. They have been strongly endorsed by the international paediatric and nutrition communities, and by agencies such as WHO and UNICEF during the last 30 years.

Growth monitoring programmes do not seem to be based on hard evidence that catch-up is beneficial, but rather on the existence of a strong association between attained size, morbidity and mortality. For example, a meta-analysis[18] showed that, compared to children with weight-for-age of ⩾80% of the NCHS growth reference, the relative risks of dying were equal to 11 for children below 60% of the reference, 3 for children between 60 and 69%, and 2 for those between 70 and 79%. Reviews on nutrition and morbidity also confirm that malnourished children are at a much higher risk of developing serious infections.[19–21]

Stronger evidence to promote early catch-up would be obtained by comparing children who (1) were born small and remained small, (2) were born small and caught up, (3) were born large and failed to grow, and (3) were born large and remained so. This led the authors to re-analyse data from a birth cohort in Brazil to investigate this association.

Subjects and Methods

In 1982, a population-based birth cohort study was started in the urban area of Pelotas, southern Brazil.[22,23] Over 99% of all births in the year were included in the study, resulting in 5914 live born infants. Information on maternal age and education, and on monthly family income, was obtained through interviews with the mothers. Children were weighed in the delivery room using regularly calibrated paediatric scales. Birth length was not measured. Verbal informed consent was obtained from parents in all phases of the study.

Mortality was monitored through regular visits to all hospitals, cemeteries, and vital registration offices in the city from 1982 to 1987. Since population mobility was high and tracing addresses was difficult, all households in the urban area (approximately 70 000) were visited in early 1984 in search of children born in 1982, who were then 20 months on average. This was repeated in early 1986 when the mean age was 42 months. In both follow-ups, mothers were interviewed using standardized questionnaires and children were weighed using portable scales (CMS Weighing Equipment, London, UK) and had their supine length (1984) or height (1986) measured using boards manufactured locally according to international specifications (AHRTAG, London, UK). Weight for age and length/height for age z-scores were calculated using the NCHS reference.[16]

Over 87% of the children were traced in 1984 and 85% in 1986. Further information on the methods and on differences between children who were located and those who were lost to follow-up are available elsewhere.[22]

Being small-for-gestational-age (SGA) was defined as a birthweight below the 10th centile of weight for gestational age of the Williams curve.[24] Gestational age was obtained by asking mothers about the date of their last menstrual period. Data on hospital admissions during 1985 were obtained by maternal recall in early 1986. Children were aged 24–35 months in January 1985. A validation sub-study showed over 90% agreement between maternal recall of causes of admission and hospital case-notes.

Catch-up growth in weight from birth to 20 months was defined as a change in z-scores of ⩾0.66, as done by Ong *et al.*[5] Average growth was defined as a change in z-scores between –0.65 and 0.65 and poor growth as a change ⩽–0.65 z-scores. This system is useful as it allows both a comparison of fast-growing children against all others and examination of dose-response.

Analytical methods included analysis of variance for continuous outcomes (z-scores of weight for age) and logistic regression for dichotomous outcomes (hospitalizations and mortality). Confounding variables included family income, maternal schooling and age (Table 1 specifies the categories used).

Results

Table 1 shows the frequency distributions of the main variables of interest for all children in the cohort as well as for those with full data for the analyses. About 9% of the children were born with a low birthweight, and the infant mortality rate was 38 per 1000 (data not shown). Of the 5914 live births, 232 are known to have died before the 1984 follow-up visit. Full data for the analyses were available for 3582 children. The main reasons for attrition were lack of information on gestational age (21%), losses to follow-up (15%) and mortality (4%). Nevertheless, the distributions of children included in the analyses are similar to those of the full cohort (Table 1); children from low socioeconomic status families and those born with a low birthweight were less likely to be included in the analyses.

Table 2 shows the mean weights for age in the 1984 and 1986 follow-up studies, according to SGA status and to weight gain

Table 1 Characteristics of the original 1982 Pelotas birth cohort and of children included in the analyses

	Per cent of children		
	Original cohort (live births)	Included in analysis	**No. of children in the analysis**
Sex			
Boys	51.3	50.9	1824
Girls	48.7	49.1	1758
Family income (in minimum wages)			
≤1	22.0	16.8	602
1.1–3	47.2	48.4	1731
3.1–6	18.4	21.6	770
6.1–10	6.4	7.0	251
>10	5.6	6.1	219
Maternal schooling (years)			
≤4	31.2	27.3	974
5–8	43.7	44.6	1594
9–11	11.1	12.0	428
≥12	14.0	16.1	575
Maternal age (years)			
<20	15.3	13.1	468
20–29	58.1	57.2	2048
≥30	26.6	29.8	1066
Low birthweight			
Yes	9.0	5.9	213
No	91.0	94.1	3369
Preterm birth[a]			
Yes	6.3	5.3	191
No	93.7	94.7	3391
Small for gestational age[a]			
Yes	14.8	14.4	516
No	85.2	85.6	3066
No. of children	5914	3582	3582[b]

[a] Information based on mothers with a known date of the last menstrual period (80% of cohort).

[b] Up to 11 children had missing values for some variables.

Table 2 Weight and height in the 1984 and 1986 follow-ups according to small-for-gestational-age (SGA) status and to weight gain patterns. *P*-values are tests for linear trend (analysis of variance)

		1984 follow-up		1986 follow-up	
Birthweight for gestational age status	**Weight gain from birth to 1984 (z-scores)**	Mean z-score of weight/age	No. of children	Mean z-score of weight/age	No. of children
SGA	≤–0.66	–2.76	29	–2.23	25
	–0.65–0.65	–1.56	205	–1.23	187
	≥0.66	–0.34	330	–0.17	304
		($P < 0.001$)		($P < 0.001$)	
AGA	≤–0.66	–0.92	1084	–0.60	973
	–0.65–0.65	–0.10	1502	–0.01	1357
	≥0.66	1.05	803	1.16	736
		($P < 0.001$)		($P < 0.001$)	

from birth to 1984. About 60% of SGA children gained more than 0.66 z-score by 1984. As expected, fast growth led to higher attained weights and, within each growth category, SGA children lagged behind appropriate birthweight for their gestational age (AGA) children. The SGA children who gained ≥0.66 z-score had effectively caught up with those who were AGA and had average growth (–0.65 to 0.65 z-score).

In Table 3, admission rates in 1985 are presented for the six categories of children. Hospitalizations were significantly less frequent for SGA children with fast growth than for those with intermediate or slow growth. The former even seemed to have lower rates than non-SGA children with slow growth, but the confidence intervals overlap. Most differences are somewhat reduced after adjustment for confounding, but the benefits of

Table 3 All-cause hospital admissions in 1985 according to small-for-gestational-age (SGA) status and weight change in the first two years of life (1982–1984). *P*-values refer to the comparison of fast-growing children versus all others

Birthweight for gestational age status	Weight gain from birth to 1984 (z-scores)	Hospital admissions in 1985[a]	Odds ratios for admission (95% CI)		No. of children
			Crude	Adjusted[a]	
SGA	≤–0.66	16.0%	3.59 (1.17–10.99)	2.54 (0.82–7.88)	25
	–0.65–0.65	16.0%	3.60 (2.16–6.00)	2.82 (1.67–4.75)	187
	≥0.66	5.6%	1.12 (0.62–2.03)	0.92 (0.51–1.67)	304
			($P < 0.001$)	($P < 0.001$)	
AGA	≤–0.66	9.2%	1.93 (1.30–2.87)	1.63 (1.09–2.43)	974
	–0.65–0.65	9.3%	1.89 (1.29–2.76)	1.74 (1.19–2.55)	1359
	≥0.66	5.1%	1.00 (reference)	1.00 (reference)	738
			($P < 0.001$)	($P < 0.001$)	

[a] Adjusted for maternal age and schooling, and family income.

catching up for SGA children become even more evident. There also appears to be an advantage of fast growth for AGA infants. *P*-levels in Table 3 refer to the original hypothesis of comparing fast-growing children (>0.66 z-scores) versus all others. One-sided tests for linear trends in proportions were also significant in the four cells of Table 3 ($P < 0.02$).

The two leading causes of admissions were acute lower respiratory infections, mostly pneumonia, and diarrhoea. Table 4 shows that SGA children who caught up were at low risk of both conditions. With the exception of the small group of 25 SGA children who grew slowly, all other results are consistent with those for all admissions. Tests for linear trend in proportions were significant for diarrhoea (both for SGA and AGA children) and for respiratory admissions among AGA children; for SGA children, the *P*-value for trend equalled 0.09.

Ten children who were seen in 1984 died before their fifth birthday and were picked up by the mortality surveillance system. Mortality rates according to the six groups presented in Tables 2–5 were respectively 34, 10, 3, 4, 1 and 0 per 1000 children, well in line with the previous results. Due to the small number of deaths, children were divided into four groups (Table 5), according to whether or not they grew faster than the mean weight gain for all children studied. Despite the wide confidence intervals, both the crude and adjusted results suggest that SGA children who caught up had similar mortality to that of AGA children, while slow-growing SGA children had the highest death rate.

Table 4 Hospital admissions in 1985 due to diarrhoea and to respiratory infections, according to small-for-gestational-age (SGA) status and weight change in the first two years of life (1982–1984). *P*-values refer to the comparison of fast-growing children versus all others

Birthweight for gestational age status	Weight gain from birth to 1984 (z-scores)	Admissions due to diarrhoea	Admission due to lower respiratory infections	No. of children
SGA	≤–0.66	0.0%	4.0%	25
	–0.65–0.65	2.1%	4.8%	187
	≥0.66	0.0%	2.3%	304
		($P = 0.06$)	($P = 0.21$)	
AGA	≤–0.66	1.5%	3.2%	974
	–0.65–0.65	0.7%	3.9%	1359
	≥0.66	0.7%	1.5%	738
		($P = 0.46$)	($P = 0.006$)	

Table 5 Child mortality (1984–1987) according to small-for-gestational-age (SGA) status and weight change in the first two years of life (1982–1984) relative to the mean weight gain for all children studied. Logistic regression analysis

Birthweight for gestational age status	Weight gain from birth to 1984 (z-scores)	Child mortality /1000[a]	Odds ratios for mortality[a] (95% CI)		No. of children
			Crude	Adjusted[b]	
SGA	Below mean[c]	13	10.46 (1.74–62.93)	8.12 (1.33–49.63)	214
	At or above mean [c]	3	2.53 (0.23–27.94)	2.13 (0.19–23.74)	302
			($P = 0.22$)	($P = 0.26$)	
AGA	Below mean[d]	2	1.89 (0.35–10.31)	1.46 (0.27–7.99)	1572
	At or above mean[d]	1	1.00 (reference)	1.00 (reference)	1499
			($P = 0.8$)	($P = 0.8$)	

[a] Overall *P*-value for the comparison of the four groups: $P = 0.048$ (crude) and 0.08 (adjusted). Test for linear trend: $P = 0.01$ (crude) and $P = 0.02$ (adjusted).

[b] Adjusted for maternal age and schooling, and family income.

[c] Mean value of the change in weight-for-age z-score for all SGA infants from birth to 20 months of age.

[d] Mean value of the change in weight-for-age z-score for all non-SGA infants from birth to 20 months of age.

Discussion

The present results suggest that there are clear short-term advantages for catch-up growth among SGA children in a developing country setting, both in terms of morbidity and mortality. This seems to be the first report on this association in the literature.

The study has some limitations that should be borne in mind when interpreting the findings. The follow-up rate was reasonably high for an urban developing-country setting, but about 15% of the children could not be traced. It is reassuring, however, that over 80% of the children in every family income and birthweight category were successfully traced.[22] Another limitation is that gestational age was assessed on the basis of the last menstrual period, and that one in five mothers was unable to provide this information. Ultrasound exams were uncommon when the study was carried out, and there was no standardized examination of the newborn. Finally, the study of hospital admissions may have been affected by Berskon bias, as malnourished children may have been more likely to be admitted than well-nourished children with the same severity of illness. However, it is reassuring that mortality trends were similar, and that adjustment for two strong covariates of nutritional status—family income and maternal education—did not affect the results.

Another possibility of bias is that chronic diseases could impair catch-up growth and also lead to more hospital admissions. However, the effect remained when the analyses were limited to the two main acute conditions leading to hospitalizations, lower respiratory infections and diarrhoea.

Two observations deserve special attention. Hospital admission rates were identical (16%) for slow- and average-growing SGA infants, while it would be expected that the latter should have presented lower rates. The same finding was present among AGA babies. Secondly, the findings on lower respiratory morbidity suggest that rapid postnatal growth may improve lung function among children with less well-developed respiratory tract architecture.

These results support the efforts of the international paediatric community to promote fast growth among children who are born small. There appear to be clear advantages of catching up in the first couple of years of life. If the recent studies from developed countries mentioned above are correct, however, there could also be long-term negative consequences from such catch-up growth. Of particular relevance are the findings of the recent Finnish study[13] showing that rapid growth in infancy was associated with a lower risk of coronary disease, while rapid growth after infancy in babies who were thin at birth was associated with a higher risk. Further research is required to document the magnitude, and not only the statistical significance, of associations between fast growth in early life and chronic disease in adulthood. The present study design did not allow the investigation of the effect of late catch-up on child health.

The possible negative effects of early catch-up for adults are supported by findings from a 25% sample of the 1982 cohort who were examined at the age of 15 years. Prevalences of overweight—defined as above the 85th percentile of the sex- and age-specific body mass index[16]—for the four groups listed in Table 5 were 9.3% for SGA children with slow growth, 16.7% for those with fast growth, 16.0% for non-SGA children with slow growth and 27.2% for those with fast growth (unpublished preliminary results).

The possible trade-off between the positive effects of catch-up on child health and its negative impact on adults must take into account the epidemiological setting. In the presence of high infant and child mortality rates, catch-up would be advantageous, while in developed countries with low under-5 mortality the long-term risk of chronic diseases may outweigh the benefits of catch-up. Timing is also relevant: other things being equal, a positive short-term impact on child survival may offset a similar negative impact on adult mortality. Finally, there are important practical considerations. If the disadvantages of catch-up in wealthy societies are confirmed, how will parents react to advice on keeping their SGA babies small through childhood? This highlights the need for interventions to improve fetal growth rather than attempting to restrict the postnatal growth of SGA children.

Further research is required to confirm both the short- and long-term consequences of catch-up growth among SGA infants. Existing datasets from both developed and developing countries should be re-analysed for this purpose.

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KEY MESSAGES

- Some recent studies on infants who were born small and presented rapid growth in childhood suggest that they face increased risk of chronic diseases in adulthood.
- We show that rapid weight gain up to two years of life is associated with a lower risk of hospital admissions, and possibly with lower mortality.
- These findings apply both to babies who were small for gestational age and for those who were not.
- Rapid growth in childhood is associated with short-term benefits, which will have to be weighted against its possible long-term disadvantages.

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Commentary: Early 'catch-up' growth is good for later health

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The importance of events before birth for lifetime health has been observed and confirmed in many populations.[1–5] In the past when infectious diseases were even more common than today it was self-evident that non-optimal early growth affected health later in life. Recent findings point towards the importance of events during critical periods of growth and development in the pathogenesis of many non-communicable diseases, e.g. coronary heart disease (CHD) and type 2 diabetes.[6–8] It is now well established that the development of a fetus in an abnormal intrauterine environment implies structural and functional adaptations with long-lasting consequences for the metabolism of that offspring in later life. These consequences are thought to be caused by biological programming.

The original 'fetal origins of adult disease hypothesis' postulates that impaired fetal growth may predispose individuals to heart disease in later life. In the original observations from Hertfordshire, UK, death from ischaemic heart disease was more common in men who had been small at birth and who were small at one year of age.[1,9]

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Individuals exposed to undernutrition *in utero* seem to be more susceptible to CHD and type 2 diabetes if they 'catch-up' in weight and body mass index during childhood. This means that the risk associated with small size at birth is modified by later growth.[5–8] Those having the highest risk for CHD and type 2 diabetes are those who were small at birth but changed 'channels of growth' during childhood.

The paper by Victora and coworkers in this issue of *International Journal of Epidemiology* focuses on the interesting and controversial role of 'catch-up' growth with regard to long-term health outcomes in individuals born small.[10] In the study by Victora *et al.* there are obvious short-term advantages of 'catch-up' growth among small-for-gestational-age (SGA) infants. There was less hospitalization for SGA children with fast growth than for those with intermediate or slow growth during infancy. This observation is of extreme importance since malnutrition in early life is a widespread health problem and promoting weight gain in infancy is standard medical practice. The impact of the problem is easy to understand knowing that approximately one-third of the world's children suffer from protein-energy malnutrition.

The early patterns of growth that predispose to adult diseases are complex. Previous studies have shown that 'catch-up' growth might well have detrimental long-term consequences. The reason for this is however not known. Those studies showing a negative effect of rapid childhood growth have focused mainly on growth from 7 years onwards.[5–7]

The importance of distinguishing between early and late 'catch-up' growth is nicely stressed by Victora *et al.*[10] Early 'catch-up' growth appears to be beneficial based upon the Brazilian study. In line with this, rapid weight gain in infancy reduced later CHD risk among Finnish men thus supporting the notion of long-term positive health benefits of early 'catch-up' growth.[8]

Many previous studies have not been able to distinguish between early and late 'catch-up' in growth—probably the main underlying cause of the controversy regarding long-term effects of 'catch-up' growth. The most unfavourable growth pattern seems to be small body size or thinness at birth, continued slow growth in early childhood/infancy and thereafter acceleration in growth. The present findings add to the evidence that protection of fetal and infant growth is a key area in strategies for the prevention of many non-communicable adult diseases.

It is easy to agree with the authors that early catch-up growth is beneficial but the other side of the coin is obesity in childhood and later life.[10] Those most vulnerable seem to be those with fast growth in childhood. Further health benefits will therefore come from preventing rapid increase in weight *after infancy.*

The thrifty phenotype hypothesis suggests that the fetal nutritional environment has a programming effect on such things as glucose and lipid metabolism and blood pressure and consequently health in adult life.[11] The mismatch between the relatively poor intrauterine environment and a nutritionally rich environment in later life is supposed to increase the risk of type 2 diabetes and many other related non-communicable diseases. Adaptation to undernutrition *in utero* may limit the extent of dietary change to which a generation can be exposed without adverse effects.

However, in most cases adult non-communicable diseases are not programmed *per se* but the tendency towards disease is programmed. Therefore it is important to consider impaired early growth as one risk factor for adult disease—not as a causative factor. These early risk factors are to a large degree modified by both biological and social factors during childhood and adult life.

If fetal and maternal nutrition are important determinants of future disease this area has major implications in the prevention of non-communicable diseases. Presently we do not know what the effects would be of providing adequate nutrition to pregnant women. Only future research will tell us whether improving the body compositions and diets of young women is to be one of the strategies for preventing type 2 diabetes and closely related non-communicable diseases. This is a very complex area and one must always bear in mind that fetal growth is also regulated by hormones, growth factors, and placental function —not only by availability of food—and this again introduces an array of other factors responsible for fetal growth.

However, lifestyle from the cradle to the grave matters. It has recently been shown that a lifestyle intervention programme (diet and exercise intervention) among adults with impaired glucose tolerance reduced the 6-year cumulative incidence of type 2 diabetes by 58%.[12] The public health implications of these results are wide.

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