A Twin Study of Cognitive Costs of Low Birth Weight and Catch-up Growth

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Objective To investigate whether there is an association between catch-up growth and cognitive performance in humans.

Study design Catch-up growth was defined as the change in weight standard deviation scores during the first 2 years of life. Cognitive performance was assessed with psychometric IQ tests, administered at ages 12 and 18 years. Data were collected in twin pairs, and analyses were carried out within pairs.

Results There was a significant negative association between catch-up growth and IQ at both ages 12 and 18 years.

Conclusions A larger gain in weight during the first 2 years of life is associated with a lower IQ. However, catch-up growth is correlated with birth weight and this correlation may explain part of the association. *(J Pediatr 2009;154:29-32)*

Several studies have demonstrated a positive association between weight at birth and childhood IQ.[1-5] We showed in a twin study that part of the positive association between birth weight and childhood IQ may be mediated by genetic effects.[2] We are interested whether there is any relation between catch-up growth and cognition, because a recent study reported that in zebra finches the level of compensatory growth after a period of poor nutrition was associated with long-term negative consequences for cognitive function.[6] During the early post-hatching period, same-sex sibling pairs of zebra-finches were exposed to 2 different nutritional environments: a normal diet or a low-quality diet. After 20 days, normal nutrition was restored in the deficit member of a pair. The degree of growth depression, the degree of compensatory growth when normal nutrition was restored, and subsequent learning performance in adulthood were linked to each other. Within pairs, the size of compensatory growth was negatively related to learning speed, but the hypo-caloric diet itself and the amount of early growth depression were not related to learning speed. In humans, early postnatal catch-up growth and excessive childhood weight gain have been related to obesity and an increased risk of adult cardiovascular disease and type 2 diabetes mellitus.[7-9] A remaining question is whether catch-up growth also influences cognitive function. In this paper, we describe the role of catch-up growth during the first 2 years of life on IQ scores at ages 12 and 18 years. Between the third trimester of pregnancy and the age of 2 years, there is a so-called critical spurt in brain growth.[10] With human sibling pairs (twins), we aimed to replicate the experimental design of the zebra finches study in humans. Same-sex twin pairs provide an ideally matched sibling pair because they share not only pre- and post-natal maternal and family factors, but also sex and age. In addition, monozygotic (MZ) pairs share 100% and dizygotic (DZ) pairs 50% of their genotype. We asked whether intra-pair differences in catch-up growth correlate with intra-pair differences in IQ. We hypothesized a negative relationship between change in weight during the first 2 years of life and IQ scores at age 12 and 18 years.

METHODS

Participants

Two groups of twin pairs were recruited through the Netherlands Twin Register (NTR).[11-13] The first group is part of a longitudinal project on physical and mental development. Cognitive ability was assessed at the ages of 12.0 years (SD, 0.1) and 18.0

DZ	Dizygotic	WISC-R	Wechsler Intelligence Scale for Children-Revised
MZ	Monozygotic	WAIS	Wechsler Adult Intelligence Scale
NTR	Netherlands Twin Register		
SDS	Standard deviation score		

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Supported by NWO (VENI: 451-04-034), NWO 575-25-012, NWO 575-25-006, NWO/SPI 56-464-14192, NWO Genomics, and NWO 480-04-004. Educational grant provided by Ferring Pharmaceuticals, The Netherlands. The authors declare no conflicts of interest.

Submitted for publication Dec 28, 2007; last revision received May 8, 2008; accepted Jul 11, 2008.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2008.07.016

years (SD, 0.2). Data from opposite-sex DZ twin pairs were excluded for 203 same-sex pairs. The second group of 149 same-sex twin pairs participated in a study of cognition and attention. The age of the second sample was 12.4 years (SD, 0.2). Zygosity was determined on the basis of DNA polymorphisms or blood group polymorphisms in 98.6% of the twin pairs and for the other twin pairs by questionnaire items on similarity.[14,15] The agreement between zygosity assigned by the replies to the questions and zygosity determined with DNA markers/blood typing is around 93%.[16]

Intelligence Tests

In the first group, IQ data were available for 154 same-sex complete twin pairs at age 12 years and for 140 pairs at age 18 years (overlap is 91 pairs). At age 12 years, the twins completed the entire Wechsler Intelligence Scale for Children-Revised (WISC-R), Dutch version.[17] At age 18 years, 11 of the 14 subtests of the Wechsler Adult Intelligence Scale (WAIS-III), Dutch version, were used.[18] From these 11 subtests, 4 index scores were derived. Full-scale IQ was derived as the composite score of these 4 index scores. For further details on the assessment procedure in this group, see Bartels et al[13] and Hoekstra et al.[15] In the second group, IQ data were available for 149 complete same-sex twin pairs. Six subtests from the WISC-R, Dutch version were used.[17] Standardized scores of this shortened form of the WISC correlate 0.94 with standardized IQ scores based on all subtests of the WISC-R.[14,19,20]

Growth Data

Catch-up growth was calculated as the standard deviation score (SDS) for weight at 2 years of age minus the SDS for weight at birth.[7] For example, when weight at 2 years was 0.5 SD below the mean reference value for that age and birth weight was 1.5 SD below the mean reference value, then the catch-up growth was +1 SDS. Information on birth weight and gestational age was collected by using questionnaires at the time of registration of the twins. Weight data at age 2 years were obtained from the Dutch National Health Services. We selected the measurement between the age of 1.5 and 2.5 years closest to the age of 2.0 years. Weight data at age 2 years were standardized dependent on sex and age by using the Dutch reference growth charts for the general population from 1997.[21] SDS for weight were calculated with the software package Growth analyser 3.[22] For weight at birth, we used the reference data of Niklasson et al[23] with correction for gestational age. When birth weight SDS or weight SDS deviated 2.5 SDs from 0, data were checked for data-entry errors.

From the first sample, we excluded 1 pair because of extreme values and 53 pairs because of incomplete weight data. From the second sample, 19 twin pairs were excluded because of incomplete data. Finally, from the first sample, 109 pairs aged 12 years and 116 pairs aged 18 years (overlap, 76 pairs) were available for analysis, and from the second sample, 130 pairs were available. The first sample consisted of 55 MZ and 54 DZ twin pairs at the age of 12 years and 60 MZ and 56 DZ twin pairs at the age of 18 years. The second sample was composed of 82 MZ and 48 DZ twin pairs.

Data Analysis

SPSS-12 software was used to perform the descriptive analyses and the paired *t* test (SPSS Inc). The paired *t* test was used to compare twins with the lowest catch-up growth from each pair with their co-twins with the highest catch-up growth. When catch-up growth was equal within a twin pair, the twin pair was excluded for the *t* test analyses. To avoid birth order effect from interfering with our analyses, twin-1–twin-2 status within a pair was randomly assigned by using SPSS. Intra-pair differences for catch-up growth and IQ were computed by subtracting the scores of twin-1 from those of twin-2. Correlations and their 95% CIs were estimated between the intra-pair differences in catch-up growth or birth weight SDS and IQ by using the statistical package Mx.[24]

RESULTS

The mean gestational age of all twins from both samples was 36.9 weeks (SD, 2.4), with a minimum of 29 weeks and a maximum of 41 weeks. Sixty percent of the twin pairs were born at term (gestational age ≥37 weeks). For each twin pair, the twin with the highest and the lowest catch-up growth was identified. For these groups, Table I provides means and SDs for catch-up growth, birth weight, birth weight SDS, weight SDS, and IQ. One pair from the second sample had to be excluded from these analyses because the catch-up growth of both twins was equal. Twins with the lowest catch-up growth within a pair were significantly heavier at birth. At age 2 years, they had a significantly lower catch-up growth than their co-twins who had lower birth weight. Table II shows significant negative correlations between intra-pair differences in catch-up growth and IQ at age 12 years (both samples) and 18 years. Thus, within pairs, a larger gain in weight during the first 2 years of life is associated with a lower IQ. Within twin pairs, differences in birth weight SDS were significantly and positively associated with differences in IQ at ages 12 and 18 years (Table II), confirming earlier observations that the twin who is heavier at birth has higher IQ scores later in life. Birth weight SDS and catch-up growth were significantly negatively correlated in both samples and the correlation did not differ in the 2 samples (r = -0.71; χ^2_1, $P = .48$). A paired *t* test showed that co-twins with the lowest birth weight were significantly lighter at age 2 years. They had a significantly higher catch-up growth and lower IQ scores at age 12 years than their co-twins with the highest birth weight ($P < .01$).

Excluding twin pairs with a gestational age <37 weeks from the analysis did not systematically effect on the association between catch-up growth and IQ (Table II). Confidence intervals of both correlations show a large overlap. Therefore, prematurity appeared not to be of major importance in the association between catch-up growth and IQ.

Table I. Means and standard deviations for catch-up growth, birth weight (g), birth weight standard deviation scores, standard deviation scores for weight at age 2 years, and full-scale IQ for twins with the lowest and the highest catch-up growth

	Sample	N	Lowest catch-up growth	Highest catch-up growth	P value
Catch-up growth	I	149	0.42 ± 1.05	1.01 ± 1.17	<.001
	II	129*	0.39 ± 1.02	1.09 ± 1.06	<.001
Birth weight	I	149	2594 ± 472	2398 ± 478	<.001
	II	129*	2657 ± 503	2424 ± 530	<.001
Birth weight SDS	I	149	−0.68 ± 0.92	−1.18 ± 0.99	<.001
	II	129*	−0.58 ± 0.88	−1.18 ± 0.98	<.001
SDS weight age 2	I	149	−0.26 ± 0.95	−0.17 ± 1.05	.12
	II	129*	−0.19 ± 1.00	−0.09 ± 1.00	.098
IQ 12 years	I	109	101.3 ± 12.7	100.5 ± 12.3	.41
	II	129*	101.6 ± 15.3	98.4 ± 13.4	.002
IQ 18 years	I	116	102.1 ± 8.9	101.8 ± 8.8	.67

*One pair had to be excluded because the catch-up growth within the pair was equal.

Table II. Pearson correlations between intra-pair differences in catch-up growth/birth weight standard deviation scores and intra-pair differences in IQ

	Sample	n		Correlation in all pairs (95% CI)	P value	n		Correlation in pairs with GA ≥ 37 weeks (95% CI)	P value
IQ age 12 years	I	109	ΔCUG-ΔIQ	–0.21 (–0.37-0.04)	χ^2_1 = 3.51 P = .02	64	ΔCUG-ΔIQ	−0.32 (–0.50-–0.11)	χ^2_1 = 8.24 P = .004
			ΔBW-ΔIQ	0.24 (0.06-.040)	χ^2_1 = 6.728 P = .009		ΔBW-ΔIQ	0.36 (0.14-0.54)	χ^2_1 = 9.73 P = .002
	II	130	ΔCUG-ΔIQ	–0.28 (–0.43-–0.12)	χ^2_1 = 10.82 P = .001	81	ΔCUG-ΔIQ	−0.23 (–0.41-–0.02)	χ^2_1 = 7.24 P = .007
			ΔBW-ΔIQ	0.25 (0.09-0.40)	χ^2_1 = 7.82 P = .005		ΔBW-ΔIQ	0.24 (0.03-0.42)	χ^2_1 = 5.05 P = .025
IQ age 18 years	I	116	ΔCUG-ΔIQ	−0.22 (–0.38-–0.05)	χ^2_1 = 6.41 P = .01	68	ΔCUG-ΔIQ	–0.29 (–0.47-–0.08)	χ^2_1 = 4.74 P = .029
			ΔBW-ΔIQ	0.24 (0.07-0.40)	χ^2_1=8.96 P = .003		ΔBW-ΔIQ	0.26 (0.06-0.45)	χ^2_1 = 6.25 P = .001

ΔCUG-ΔIQ, Intra-pair differences in catch-up growth and intra-pair differences in IQ; *ΔBW-ΔIQ*, intra-pair differences in birth weight SDS and intra-pair differences in IQ; *GA*, gestational age.

The correlations between intra-pair differences in catch-up growth and IQ were similar in MZ and DZ pairs, suggesting that this association may not be mediated by genetic effects (data not shown).

DISCUSSION

We investigated the relation between catch-up growth and cognitive ability in humans. Like in the "zebra finch study," we used a family design with pairs of siblings (twins) to evaluate the association between catch-up growth and IQ. Intra-pair analyses are ideal for this type of research; the co-twin provides the matched control, and no confounding factors, such as maternal height and IQ, parental social class, or diet, have to be controlled for.

Our results showed that within pairs there was an inverse association between catch-up growth and IQ at the ages of 12 and 18 years. The twin showing more catch-up growth in weight during the first 2 years of life had lower IQ scores both at ages 12 and 18 years. The correlations were modest, with values between −0.2 and −0.3. The association was not caused by an effect of prematurity, because excluding prematurely born twins gave similar results.

Our study, however, illustrates the difficulty in differentiating the effects of birth weight from the effects of catch-up growth. Generally, children with a lower birth weight show more catch-up growth. An interesting question is whether the relation between catch-up growth and IQ can be explained by birth weight or by a combination of birth weight and catch-up growth. Fisher et al were able to manipulate the nutritional environment and induce compensatory growth in zebra finches.[6] They could separate the effects of growth during nutritional deficit from the effects of compensatory growth, because these 2 effects were not significantly correlated. We tried to distinguish the effects associated with birth weight from those of catch-up growth by looking in a subgroup of the 12-year-old twins, those with comparable birth weight (difference in birth weight ≤165 g; n = 83 pairs). The association between intra-pair differences in catch-up growth and IQ was negative (r = −0.18), but did not reach statistical significance (*P* = .10). However, this finding is in line with our theory that catch-up growth may have a negative effect on cognitive development. Unfortunately, the subgroup was small, and these analyses require larger samples. A design with a large number of twins of comparable birth weight discordant for catch-up growth is needed to elucidate the role of catch-up growth and separate it from the effect of birth weight.

A limitation because of ethical reasons is that catch-up growth cannot be induced in humans by creating a nutritional deficit and comparing these individuals to others receiving a normal diet. Therefore research with animal models can help us to clarify the role of catch-up growth. There are several studies that related nutrient-enriched diet to better cognitive outcome,[25-28] but these studies looked at the association between diet and cognitive function rather than compensatory growth and cognitive development. A study in full-term babies who were small for gestational age compared the effect of standard formula and enriched formula on neurodevelopment.[29] Children who were fed with enriched formula had greater gains in length and head circumference, but had poorer neuro-developmental outcome at 9 months of age. This was especially marked in girls, who showed the greatest compensatory growth. These findings support our results that catch-up growth may have negative effects on cognitive abilities. However, the developmental disadvantage at 9 months was not seen at the age of 18 months.

Adequate caloric intake is needed for proper brain growth and cognitive development, particularly in preterm infants requiring higher caloric intake. However, promoting nutrient-enriched diets to induce catch-up growth should be done with caution because catch-up growth has not only been associated with obesity and disease in later life, but also may have a negative effect on cognitive development. The mechanism by which increased physical growth rates may adversely affect cognitive function is still unclear. Compensatory growth may require more energy, which could come at the expense of neural development. Another possibility is that a period of catch-up growth induces a kind of stress, which may impair hippocampal function. The hippocampus is important for processes of learning and memory. Stress is known to alter hippocampal plasticity and memory in a negative way.[30] Recently, early calorie intake was related to caudate volumes and IQ.[31] The high-nutrient group had larger caudate volumes and higher verbal IQ scores The association between compensatory growth and neurodevelopmental outcome could relate to the caudate nucleus.

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