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Catch-up growth in children with late-diagnosed coeliac disease

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Anthropometric parameters and catch-up growth were prospectively evaluated in fifty late-diagnosed children with coeliac disease aged 2·25–10 years after 1–4 years of adhering to a strict gluten-free diet (GFD). The anthropometric parameters were expressed as *Z* scores relative to National Centre for Health Statistics standards using Epi Info 2000 (weight-for-height *Z* score (WHZ) and height-for-age *Z* score (HAZ)). Catch-up growth was evaluated by repeated measures. ANOVA, overall significance by an *F* test and pair-wise comparisons for estimated marginal means using the least significant difference. At the time of enrolment, no significant difference was observed in WHZ and HAZ between children diagnosed before (group 1) or after (group 2) 4 years of age. On follow-up, HAZ was significantly higher in group 1 after the first and third years of the GFD ($P=0·04$ and 0·02, respectively), with a non-significant increase after completing 4 years of the GFD ($P=0·22$). Feeding the GFD resulted in an overall significant ($F=3·99$, $P=0·011$) increase in HAZ up to 4 years of follow-up. However, the catch-up in height was incomplete, with stunting in sixteen (55·4 %) of twenty-nine children after 3 years and in seven (46·6 %) of fifteen children after 4 years on the GFD. Pair-wise comparisons demonstrated a linear catch-up growth during the initial follow-up on GFD. Treatment with the GFD did not result in an overall significant increase in WHZ up to 4 years of follow-up ($F=1·01$, $P=0·42$). Our results suggest that, in children with late-diagnosed coeliac disease, treatment with a GFD leads to a normalisation of body mass and a significant but incomplete recovery in HAZ during 4 years of follow-up.

Catch-up growth: Gluten-free diet: Gluten enteropathy: Coeliac disease

Coeliac disease (CD) is increasingly being diagnosed as an important cause of malabsorption in Indian children (Kumar *et al.* 1993; Yaccha *et al.* 1993; Patwari *et al.* 2003). Classically, CD presents at between 9 and 10 months of age (Walker Smith, 1985), but studies have now emphasised the changing pattern of presentation of CD over recent years (Maki *et al.* 1988). Cases of late-diagnosed monosymptomatic CD presenting with short stature as the only manifestation have been more frequently reported (Grikk *et al.* 1980; Rosenback *et al.* 1986). Most of the Indian studies have also reported a delayed diagnosis of CD (Kumar *et al.* 1993; Poddar, 1999; Patwari *et al.* 2003), which could be due to delayed weaning, a late introduction of gluten, delayed referral and lack of awareness about the disease. When CD is diagnosed early, the introduction of a gluten-free diet (GFD) promotes an accelerated growth rate (Rea *et al.* 1996), and normal height is reached in 12 months (Cataldo *et al.* 1987) to 2 years (Barr *et al.* 1972). The real duration of catch-up growth in the late-diagnosed CD patients is, however, not well defined (Bosio *et al.* 1990).

The exclusion of gluten from the diet modifies dietary composition, exposing children with CD to nutritional imbalance. This imbalance may be compounded in developing countries such as India as a result of poor access to nutritionally suitable alternatives for wheat. There is a paucity of data on the effects of a GFD on growth in children with CD in India. The present study aimed to assess catch-up growth in children with a delayed diagnosis of CD.

Materials and methods

Children of either sex diagnosed as having CD based on the modified European Society of Pediatric Gastroenterology and Nutrition criteria (Working Group of the European Society of Pediatric Gastroenterology and Nutrition, 1990) were prospectively studied. Diagnosis was also supported by a positive serology for CD (antigliadin antibody IgG and IgA, anti-endomysial antibody IgA). Children diagnosed with CD were started on a GFD and followed up in the Paediatric Gastroenterology and Nutrition Clinic. Children were encouraged to attend this clinic every month for the first 6 months, every 2 months over the following 6 months, quarterly for the next year and every 6 months thereafter. On regular follow-up, the children were assessed for details of diet (to ascertain compliance and quality of food intake), symptomatic improvement and anthropometric assessment. Children with irregular follow-up who had taken the GFD for less than 6 months or with doubtful compliance were excluded from the final analysis.

Anthropometric assessment

Body weight was determined by subjects standing bare foot in light clothing on a digital scale. While recording the weight, shoes, long trousers, sweaters and other heavy clothing were removed. Weight was recorded to the nearest 100 g. Height

Abbreviations: CD, coeliac disease; GFD, gluten-free diet; HAZ, height-for-age *Z* score; WHZ, weight-for-height *Z* score.

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without shoes was measured with a wall-mounted stadiometer graded in centimeters with the head in the Frankfurt plane. The height was recorded to the nearest 0·1 cm.

Socioeconomic status was assessed by:

- monthly family income;
- the educational status of the parents, graded according to a previously described score (Kappu Swamy, 1976), the sum of the graded educational scores of the father and mother being used for statistical analysis;
- the total number of dependents;
- the birth order of the child.

The official Wholesale Price Index for all the commodities during the corresponding years was taken into consideration to adjust for income the categories outlined in the score.

Gluten-free diet

In northern India, wheat is the staple diet and is taken in the form of 'chapati' (Indian bread made of unleavened wheat dough prepared on a griddle). As gluten-free wheat is not available in our hospital or in the open market, the GFD consisted of 'chapati' made of soyabean–rice flour (1:3 w/w protein 15 g, energy 366 kJ per 100 g), rice–bengal gram flour (1:1 w/w protein 11·9 g, energy 352 kJ per 100 g) or maize–soyabean flour (3:1 w/w protein 19·1 g, energy 364 kJ per 100 g). During hospitalisation, the GFD was prepared in the hospital kitchen and distributed free of cost. The families were shown how to make 'wheat-free chapatis' in the hospital, and after discharge from the hospital the GFD was prepared and served by the families themselves. In view of a potential risk of adulteration with wheat particles while milling the non-wheat cereals, the families were specifically counselled to mill the rice, soyabean, maize or bengal gram in special mills or in a domestic mixer.

Compliance with the GFD was ensured by a thorough counselling of all the family members (school teachers as well when requested by the parents or deemed necessary by the investigators), and accidental ingestion was prevented by forbidding foodstuffs known to contain gluten and checking the composition and commercial labels of all unknown food items, including toffees, chocolates, ice creams, juices, etc. All the children received Fe and folic acid supplementation.

Statistical analysis

For statistical comparison, height-for-age and weight-for-height were expressed as *Z* scores (HAZ and WHZ, respectively) relative to National Centre for Health Statistics standards (Hamill *et al.* 1979) using the computer software package Epi Info 2000. The maximum height and age limitations for WHZ calculation (age: boys 11·5 years, girls 9 years; maximum height: boys 145·0 cm, girls 137 cm) were taken into consideration, and these cases were excluded from statistical analysis (Gorstein *et al.* 1994). Cut-off points for defining malnutrition as the *Z* score from the reference median included HAZ -2 to -3 (moderate stunting) and <-3 (severe stunting), and WHZ -2 to -3 (moderate wasting) and <-3 (severe wasting) (Cartson & Wardlaw, 1990).

Evaluation of catch-up growth for up to 4 completed years based on WHZ and HAZ for between-subject factors such as age and sex was performed while adjusting for the educational scores of parents, family income, the number of dependents and the birth order using repeated-measures ANOVA. SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis. The overall significance of catch-up growth using WHZ and HAZ was evaluated by the *F* test. The pair-wise comparisons for estimated marginal means at different completed years of follow-up were made using least significant difference. A value of $P<0·05$ was taken as significant.

Results

General characteristics

Sixty children (thirty-eight girls and twenty-two boys) aged 2·25–12 years of age (mean 7·6 (SD 2·37) years) entered the study and were started on a GFD. The children enrolled came from urban areas around Delhi as well as rural and semi-urban and rural areas of the neighbouring states. These children belonged to upper middle and lower middle as well as poor socio-economic classes. The duration of their symptoms prior to diagnosis ranged from 3 months to 10 years (mean 5·8 (SD 2·6) years). Stunted growth (100 %), pallor (100 %) and diarrhoea (91·6 %) were the predominant clinical features at the time of diagnosis of CD. Fifty children (83 %; thirty-three girls and seventeen boys) aged 2·25–10 years at diagnosis (mean 5·46 (SD 2·3) years) who regularly attended for follow-up and showed strict dietary compliance were included in the assessment of catch-up growth after the GFD had been instituted. Therefore, at the time of assessment of catch-up growth, fifty children (100 %) had completed 1 year, forty (80 %) 2 years, twenty-nine (58 %) 3 years and fifteen (30 %) 4 years of the GFD.

Age at diagnosis. The effect of a delayed diagnosis of CD on nutritional indicators was studied by dividing the study group into two age groups. The study group comprised children who had been diagnosed between 2 and 4 years of age (group 1) and those diagnosed after the age of 4 years (group 2). At the time of diagnosis of CD, the mean WHZ and HAZ of the children in group 1 (*n* 19) were relatively higher than those of group 2

Table 1. Age of diagnosis of coeliac disease and nutritional indicators† after 1, 2, 3 and 4 years of a gluten-free diet (GFD)

	Group 1 (2–4 years)		Group 2 (> 4 years)		
	Mean	SD	Mean	SD	*P* value
At the time of diagnosis	*n* 19		*n* 31		
WHZ S	−1·08	1·20	−1·34	1·33	0·48
HAZ S	−3·10	1·29	−3·85	1·59	0·07
Completed 1 year on GFD	*n* 19		*n* 31		
WHZ 1	0·43	0·92	0·68	1·04	0·39
HAZ 1	−2·29	1·25	−3·09	1·35	0·04*
Completed 2 years on GFD	*n* 15		*n* 25		
WHZ 2	1·00	1·38	0·4	1·45	0·27
HAZ 2	−1·95	1·2	−2·89	1·7	0·05
Completed 3 years on GFD	*n* 10		*n* 19		
WHZ 3	0·85	1·04	0·18	1·01	0·13
HAZ 3	−1·5	1·18	−2·64	1·27	0·02*
Completed 4 years on GFD	*n* 10		*n* 19		
WHZ 4	0·89	1·16	0·79	0·4	0·84
HAZ 4	−1·64	0·56	−2·13	0·92	0·22

* Mean values were significantly different, **P*< 0·05.

† WHZ S, WHZ 1, WHZ 2, WHZ 3, WHZ 4: weight-for-height *Z* score at the start of the GFD and after 1, 2, 3 and 4 years of the GFD, respectively. HAZ S, HAZ 1, HAZ 2, HAZ 3, HAZ 4: equivalent height-for-age *Z* scores.

Table 2. Pair-wise comparison of weight-for-height and height-for-age Z scores after 1, 2, 3 and 4 years on a gluten-free diet (GFD)

Measure	Year of completion of GFD (I)§	Year of completion of GFD (J)‖	Mean difference (I − J)	SE	Significance‡
Weight-for-height *Z* score	1	2	−1·714*	0·319	0·000
		3	−1·975*	0·350	0·000
		4	−1·702*	0·289	0·000
		5	−2·146*	0·333	0·000
	2	1	1·714*	0·319	0·000
		3	−0·261	0·195	0·193
		4	1·167E-02	0·249	0·963
		5	0·213	0·332	0·533
	3	1	1·975*	0·350	0·000
		2	0·261	0·195	0·193
		4	0·273	0·195	0·176
		5	0·597	0·326	0·095
	4	1	1·702*	0·289	0·000
		2	−1·167E-02	0·249	0·963
		3	−0·273	0·195	0·176
		5	−4·500E-02	0·251	0·861
	5	1	2·146*	0·333	0·000
		2	−0·213	0·332	0·533
		3	−0·597	0·326	0·095
		4	4·500E-02	0·251	0·861
Height-for-age *Z* score	1	2	−0·710*	0·175	0·000
		3	−1·114*	0·232	0·000
		4	−1·735*	0·183	0·000
		5	−1·676*	0·284	0·000
	2	1	0·710*	0·175	0·000
		3	−0·404*	0·170	0·26
		4	−1·025*	0·174	0·000
		5	−1·260*	0·273	0·001
	3	1	1·114*	0·232	0·000
		2	0·404*	0·170	0·026
		4	−0·622*	0·155	0·001
		5	−0·743*	0·211	0·005
	4	1	1·735*	0·183	0·000
		2	1·025*	0·174	0·000
		3	0·622*	0·155	0·001
		5	5·000E-02	0·099	0·624
	5	1	1·676*	0·284	0·000
		2	1·260*	0·273	0·001
		3	0·743*	0·211	0·005
		4	−5·000E-02	0·099	0·624

*Mean values were significantly different, *$P<0·05$.
‡ Adjustment for multiple comparisons: least significant difference (equivalent to no adjustments).
§ 1, on enrolment; 2, after 1 year of GFD; 3, after 2 years of GFD; 4, after 3 years of GFD; 5, after 4 years of GFD.
‖ 1, on enrolment; 2, after 1 year of GFD; 3, after 2 years of GFD; 4, after 3 years of GFD; 5, after 4 years of GFD.

(*n* 31; Table 1), but the differences were statistically insignificant ($P=0·48$ and 0·07, respectively).

Overall catch-up growth and pair-wise comparisons. Table 2 shows the pair-wise effective mean differences of WHZ and HAZ and their significance between different years of completion of the GFD obtained from repeated-measures ANOVA.

In terms of height-for-age, twenty-nine (58 %) of the fifty children at diagnosis had an HAZ <-3 SD, twelve (24 %) had a score of -2 to -3 SD, and nine (18 %) had an HAZ of between -2 and 0 (Fig. 1). The mean and standard deviation for the HAZ at the time of enrolment were $-3·58$ (SD 1·56). Feeding the GFD resulted in an overall significant ($F=3·99$, $P=0·011$) increase in HAZ for up to 4 years of follow-up (Figs. 2 and 3). On pair-wise comparison, the HAZ showed a significant increase at each year of completion of the GFD compared with the previous year except between the third and fourth years of completion. The catch-up in height was incomplete as sixteen (55·4 %) of the twenty-nine children who had completed 3 years and seven (46·6 %) of the fifteen who had completed 4 years of the GFD remained stunted.

With regard to weight-for-height, thirteen (26 %) of fifty children were wasted at diagnosis, with three (30 %) severely wasted and ten (70 %) moderately wasted children. The mean WHZ score at the time of enrolment was $-1·19$ (SD 1·28). Treatment with the GFD did not result in an overall significant increase in WHZ up to 4 years of follow-up ($F=1·01$, $P=0·42$).The pair-wise comparisons in the case of WHZ indicate that the scores of children on enrolment were significantly lower than the subsequent scores. However, none of the mean differences of other pairs at later follow-ups was significant. None of the patients showed wasting at the end of the first year on the GFD. There was an overshoot in WHZ after completing the fourth year of GFD, but this was not statistically significant.

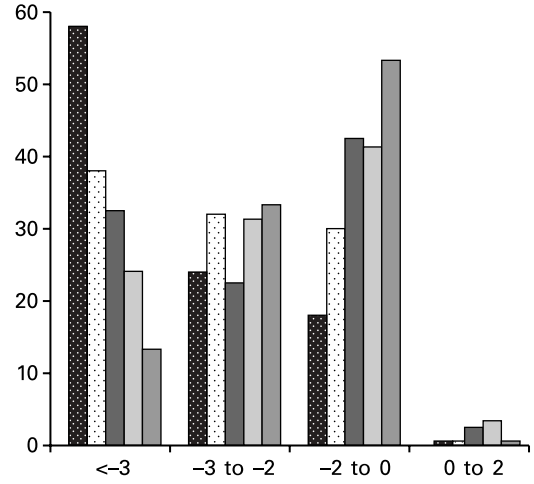

Fig. 1. Distribution of height-for-age *Z* scores at diagnosis (HAZ S) and during follow-up at 1 (HAZ 1), 2 (HAZ 2), 3 (HAZ 3) and 4 (HAZ 4) years on a gluten-free diet. ▩ Haz S (*n* 50); ▫ Haz 1 (*n* 50); ■ Haz 2 (*n* 40); □ Haz 3 (*n* 29); ■ Haz 4 (*n* 15).

Influences on catch-up growth

Age at diagnosis. The effect of a delayed diagnosis of CD on catch-up growth was studied by comparing the results of group 1 (children diagnosed between 2 and 4 years of age) and group 2 (diagnosed after the age of 4 years). There was no significant difference in WHZ in terms of the catch-up growth between the two age groups on follow-up ($P=0{\cdot}89$, 0·47, 0·533 and 0·35 at the completion of 1, 2, 3 and 4 years of the GFD, respectively). After completing the first and third years on the GFD, HAZ was significantly higher in group 1 ($P=0{\cdot}04$ and 0·02, respectively), but it was marginally higher ($P=0{\cdot}05$) after completing the second year. At the end of fourth year of the GFD, there was no significant difference in HAZ between the groups ($P=0{\cdot}22$; Table 1). However, six (66·6 %) of the nine children in group 2 but only one (16·6 %) of six children in group 1 remained stunted.

Sex. There were no significant differences between the boys (*n* 17) and girls (*n* 33) at all times when their anthropometric parameters were compared at the time of diagnosis and during follow-up.

Other covariates. There was a positive correlation between the educational status of the parents and HAZ on diagnosis of CD ($P=0{\cdot}35$) and on follow-up on the GFD until the end of the first year ($P=0{\cdot}046$). However, after the completion of the second year of GFD and thereafter, no correlation was observed between educational status and HAZ. There were one or two dependents in forty-one (82 %) of these families, and the child's birth order was one or two in forty-eight (96 %) instances. The number of dependants in the family correlated directly with the age at which CD had been diagnosed.

The interquartile range Rs 3500/- was taken as the cut-off point for family income. The mean WHZ at the start of GFD and at other follow-ups in the lower and higher income categories was not significant. However, the initial HAZ ($P<0{\cdot}001$) in these categories (−4·56 (SD 1·53) and −2·96 (SD 1·16)) and at first follow-up ($P<0{\cdot}001$) in the lower and higher income categories (−3·68 (SD 1·45) and −2·24 (SD 0·98)) was statistically significant. The differences were not significant at follow-up from the second to the fourth year.

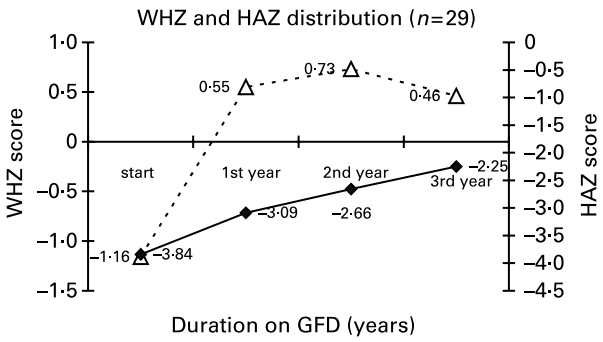

Fig. 2. Weight-for-height (WHZ; △) and height-for-age (HAZ; ◆) score distribution for twenty-nine children after 3 years on a gluten-free diet (GFD).

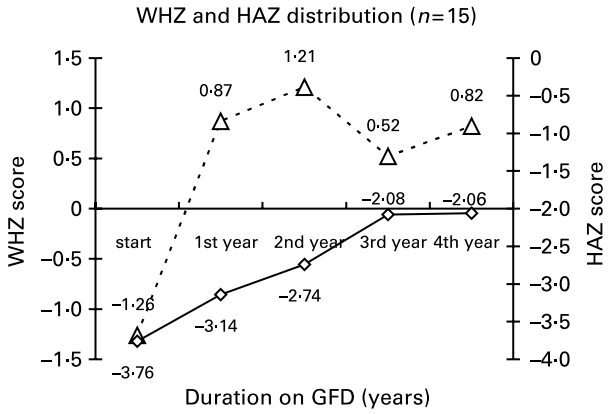

Fig. 3. Weight-for-height (WHZ; △) and height-for-age (HAZ; ◆) score distribution for fifteen children after 4 years on a gluten-free diet (GFD).

Discussion

The control of the growth process is related to many complex interacting factors, including biological characteristics such as genotype, external factors such as nutrition and environment, and internal signalling systems such as hormones and growth factors. Catch-up growth, a discontinuous process made up of a sequence of bursts of growth followed by a resting phase (Greco *et al.* 1994), is defined as rapid, compensatory growth during rehabilitation from prior nutritional deficit or illness (World Health Organization, 1995). During catch-up, the child may grow in height at up to four times the average rate for his or her chronological age. As the child approaches his or her genetically predisposed channel, the restoring force diminishes and the growth velocity again decreases (Prader *et al.* 1963; Tanner, 1981).

The nutritional rehabilitation of CD patients with a GFD leads to an acceleration in growth (Prader *et al.* 1963; Barr *et al.* 1972; Cataldo *et al.* 1987; Luca *et al.* 1988; Bosio *et al.* 1990; Hernandez *et al.* 1992; Damen *et al.* 1994). The present study also revealed an accelerated growth, manifested as a significant improvement in HAZ and WHZ, when a GFD was instituted. After the start of therapy, weight-for-height normalised at the end of first year of the GFD (WHZ

> -2 SD) and overshot during the second year of the GFD. This pattern, as reported in earlier studies (Barr *et al.* 1972; Greco *et al.* 1994), indicates that weight catches up more quickly than height, leading to a transitory status of overweight. The increase in WHZ at the end of the fourth year of the GFD could be attributed to continued weight gain. Pair-wise catch-up growth comparisons clearly demonstrated that the WHZ of children on enrolment was significantly lower than subsequent scores, but none of the mean differences of other pairs at later follow-ups was significant. HAZ, on the other hand, demonstrated a significant increase at each year of completion of the GFD compared with the previous year, except between the third and fourth years of completion of the GFD. The present results therefore suggest that there is a linear catch-up growth in terms of height during the initial follow-up on a GFD.

Barr *et al.* (1972) and others (Luca *et al.* 1988; Bosio *et al.* 1990; Hernandez *et al.* 1992; Damen *et al.* 1994; World Health Organization, 1995; Gerolamo *et al.* 1999) have reported a variability in the growth pattern of patients with CD: both a complete (Barr *et al.* 1972; Bosio *et al.* 1990; Hernandez *et al.* 1992; Damen *et al.* 1994; Greco *et al.* 1994) and an incomplete (Cataldo *et al.* 1987; Luca *et al.* 1988; Gerolamo *et al.* 1999) catch-up in height when CD is diagnosed at an early stage (less than 2 years, Barr *et al.* 1972; Damen *et al.* 1994; World Health Organization, 1995; Gerolamo *et al.* 1999) and with late diagnosis (Luca *et al.* 1988; Bosio *et al.* 1990; Damen *et al.* 1994). The present study reveals a persistence of stunting even after 4 years of the GFD; this could be due to the following:

- catch-up in height in severely stunted children takes a relatively longer time even with a favourable environment (World Health Organization, 1986);
- late-diagnosed patients show a slower and seemingly incomplete catch-up growth (Bosio *et al.* 1990);
- multiple alterations occur in the growth axis (growth hormone-binding proteins, insulin-like growth factor-1, insulin-like growth factor binding protein) during the active phase of the disease (Federico *et al.* 1997);
- negative effects of CD on growth (Gerolamo *et al.* 1999).

In the present study, children with an early diagnosis demonstrated better increments in height than children diagnosed late. This is shown by: a lower severity of stunting at diagnosis, although statistically insignificant; a higher HAZ on follow-up of 4 years; the prevalence of stunting at the end of the fourth year on the GFD (six of nine children in group 2 *v*. only one of six children in group 1). Studies have reported a complete catch-up in height (Hernandez *et al.* 1992; Damen *et al.* 1994; Luciano *et al.* 2002) if CD is diagnosed prior to 9 years of age, although patients diagnosed after the age of 2 years tend to maintain a body size slightly below the mean (Hernandez *et al.* 1992).

The correlation at diagnosis and HAZ as follow-up for 3 years could be due to the influence of environmental factors in the initial phase of catch-up growth. No correlation was observed with WHZ, which could be because of the obvious biological differences between wasting and stunting. Wasting is precipitated by infection and usually occurs in situations where food supply is limited. Stunting is frequently associated with poor overall economic conditions, especially mild-to-moderate, chronic or repeated infection, as well as inadequate nutrient intake (World Health Organization, 1986).

Studies have reported that the rate of catch-up growth would be higher if the initial statural deficit were more pronounced (Damen *et al.* 1994). In the present study as well, there was a positive correlation between HAZ on diagnosis of CD and HAZ on follow-up while receiving the GFD. HAZ at diagnosis correlated positively with educational status and family income at diagnosis and at the initial follow-up after the first year of the GFD, but the differences were statistically insignificant at other follow-ups.

In conclusion, the GFD leads to a normalisation of body mass (evaluated as weight-for-height) and a substantial improvement in height-for-age in developing countries such as India where children have minimal access to nutritionally suitable alternatives to wheat. Apart from the GFD, careful follow-up and good compliance with the dietary rules are mandatory for optimising children's growth potential. The present study highlights that there is a linear catch-up growth in terms of height during the initial follow-up on the GFD. The increments in height may be influenced by age at the time of diagnosis of CD and to some extent by the educational and economic status of the parents.

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