

# Growth rate of coeliac children is compromised before the onset of the disease

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2019-317976>).

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Received 25 July 2019  
Revised 3 April 2020  
Accepted 8 April 2020

## ABSTRACT

**Introduction** Growth impairment has often been described in children who develop coeliac disease (CD). Based on data from the multicentre, longitudinal PreventCD study, we analysed the growth patterns of infants at genetic risk of CD, comparing those who developed CD by 6 years of age (CD 'cases', 113 infants) versus those who did not develop CD by 6 years (no CD 'controls', 831 infants).

**Methods** Weight and length/height were measured using a longitudinal protocol. Raw measurements were standardised, computing z-scores for length/height and weight; a linear mixed model was fitted to the data in order to compare the rate of growth in the two cohorts.

**Results** Neither cases nor controls had significant growth failure. However, when the mean z-scores for weight and height were analysed, there was a difference between the two groups starting at fourth month of life. When the growth pattern in the first year was analysed longitudinally using mixed models, it emerged that children who develop CD had a significantly lower growth rate in weight z-score ( $-0.028/\text{month}$ ; 95% CI  $-0.038$  to  $-0.017$ ;  $p < 0.001$ ) and in length/height z-score ( $-0.018/\text{month}$ ; 95% CI  $-0.031$  to  $-0.005$ ;  $p = 0.008$ ) than those who do not develop CD. When the whole follow-up period was analysed (0–6 years), differences between groups in both weight and length/height z-scores were confirmed.

**Conclusion** The growth of children at risk of CD rarely fell below 'clinical standards'. However, growth rate was significantly lower in cases than in controls. Our data suggest that peculiar pathways of growth are present in children who develop CD, long before any clinical or serological signs of the disease appear.

## INTRODUCTION

Impaired growth is common in coeliac disease (CD), and it appears not to be fully explained by clinical features or by malabsorption of nutrients.<sup>1</sup> Growth profiles appear to be independent of gastrointestinal symptoms and anaemia. Inflammation has been suggested to be a common background of children with CD,<sup>2</sup> and many signs suggest that something is wrong much before the onset of the disease.<sup>3</sup> Notably, almost four decades ago, infants affected by CD showed a growth profile significantly below

## What is already known on this topic?

- Impaired growth, as assessed at the time of diagnosis, has long been recognised to be a common manifestation of coeliac disease (CD).
- If affected children are identified and put on a gluten-free diet, they show no growth impairment.

## What this study adds?

- Our data suggest that an altered growth pattern may manifest before any clinical or serological signs.
- Already at 4 months, before gluten introduction, infants who will eventually develop CD are about 0.5 cm shorter and 100 g lighter than their peers who will not develop CD by 6 years.

growth standards.<sup>4</sup> Inasmuch longitudinal analysis of growth revealed a peculiar 'pulsatile' velocity profile in children who developed CD.<sup>5</sup>

Saari *et al*<sup>6</sup> reported alterations of growth patterns in children before the onset of CD. A major contribution came from the Norwegian Mother and Child Cohort Study,<sup>7</sup> which analysed the growth of 440 children with CD. They found that z-scores for height at 12 months and for weight at 15–18 months were lower in children who developed CD at a mean age of 4.4 years than in a cohort of healthy children. On the contrary, the weight and length of infants in the birth cohort of the TEDDY study (The Environmental Determinants of Diabetes in the Young) did not differ between children who did and those who did not develop CD.<sup>8</sup> In addition, a study of gene expression 1 year before the production of transglutaminase type 2 antibodies in a cohort at risk of CD suggests that the molecular background of infants who develop CD years later differs from that of infants who do not develop CD.<sup>3</sup>

The PreventCD<sup>9</sup> cohort study offers a unique opportunity to monitor the growth of about 1000 newborns at genetic risk of developing CD from birth to 8 years of age across eight countries. The



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**To cite:** Auricchio R, Stellato P, Bruzzese D, *et al*. *Arch Dis Child* Epub ahead of print: [please include Day Month Year]. doi:10.1136/archdischild-2019-317976

aim of our study is to explore the growth profile of a cohort of newborns from families genetically at risk of CD, monitored regularly from birth to years of age (PreventCD).<sup>9</sup>

## PATIENTS AND METHODS

### Cohort study

The growth of 944 newborns who had a first-degree relative affected by CD was monitored from birth to 6 years of age.<sup>10</sup> Length and height were measured according to a standardised protocol at each centre, as previously described.<sup>9</sup> From January 2007 to March 2017, we collected 11450 length/height and 12666 weight measurements (average of 12 and 13 measures per child). Weight was measured to the nearest 50 g, and length/height was measured to the nearest 0.1 cm. Length/height and weight were standardised for age and sex by transforming to z-scores based on the WHO growth standards.<sup>11</sup>

### Diagnosis of CD

All children were periodically monitored for serum antigliadin and TGA (anti-transglutaminase)-IgA antibodies, total serum IgA, and symptoms of CD, according to the protocol used in the PreventCD trial.<sup>9</sup> CD was diagnosed according to the European Society for Paediatric Gastroenterology Hepatology and Nutrition criteria.<sup>12</sup>

### Sample size

About 900 individuals had to be recruited to detect a standardised difference in the growth pattern between cases and controls of 0.2, with a type I error of 0.01 and a power of 90%. The ratio of cases to controls was 1:8. We recruited 944 newborns to compensate for missing data.

### Statistical methods

Standard descriptive statistics were used to describe the characteristics of the two cohorts (median with range, mean±SD and frequencies with percentages). Significance of cross-sectional differences between groups was assessed using unpaired t-test and further quantified using the corresponding 95% CI on the difference of means.

Graphical representations of observed growth profiles were obtained using smoothing spline with cross-validation to estimate smoothing parameters.

Variability within and between infants was analysed in a hierarchical framework by fitting a linear mixed effect model to the z-scores of weight and length/height. Random intercept and random slope models were used, with time coded numerically as months from birth. Fixed factors included, beyond time, group (CD and no CD), gender and all the two-order interactions. Three-order interaction (group by gender by time) was not included in the final model as neither for weight nor length it reached statistical significance. Results of linear mixed model are expressed as estimated coefficient with the corresponding 95% CI and measure how much the difference in z-score units between the two groups increases (decreases) per month.

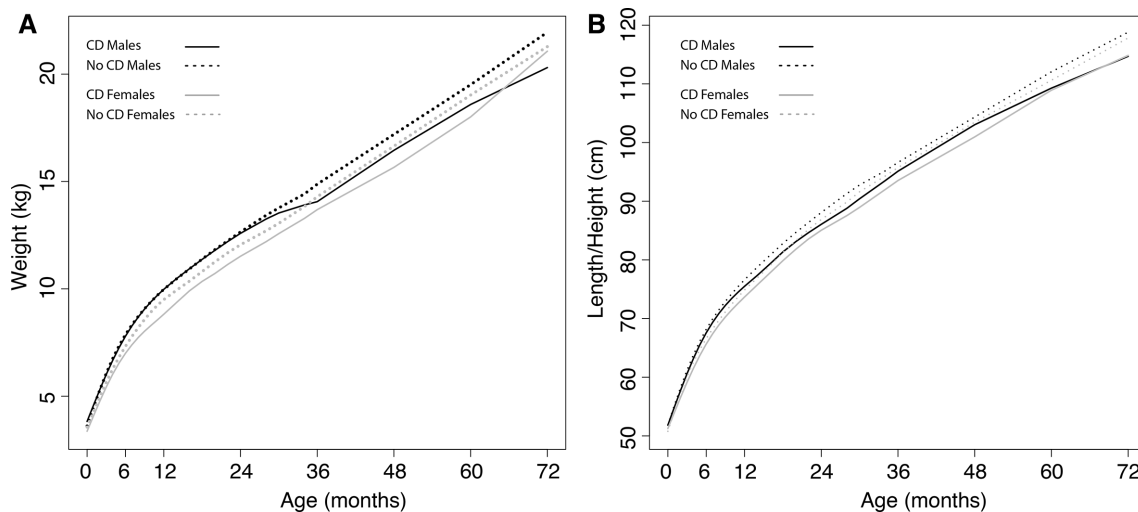
## RESULTS

On 15 March 2017, 113 of the 944 (11.9 %) children enrolled developed CD by the age of 6 years. The median age at diagnosis was 40 months. None of the children developed CD in the first year of life. Twenty children were diagnosed with CD between the ages of 12 and 24 months. Seven children had failure to thrive, defined as a clinically relevant slowing of growth rate, at the time of CD diagnosis (median age 38 months, range 20–69 months).

The frequency of low birth weight (below 2500 g) or short length at birth (below 47 cm) did not differ between the two groups.<sup>10</sup> No difference in birth weight, length or gestational age was observed between infants who developed CD (CD cases) and those who did not (no CD controls).

Figure 1 shows the mean weight and length/height of cases and controls, stratified by sex, throughout follow-up, that is, from birth to 6 years, obtained using smoothing splines. Note that the lines almost overlap, with no apparent difference between cases and controls.

Table 1 shows the mean standardised length/height and weight in the two cohorts of infants in the first 2 years; the mean differences between the two groups are also shown, with 95% CI. Although growth has to be estimated by monthly increments, in order to facilitate interpretation of data, table 1 reports the cross-sectional comparisons between the two groups. It is worth noting that at 4 months, before gluten introduction, cases were about 0.22 SD shorter (about 0.5 cm) than controls and were 0.13 SD (about 97 g) lighter, although these differences did not reach statistical significance. At 12 months cases were



**Figure 1** Smoothing splines of the average growth profile of weight (in kg, A) and height/length (in cm, B) during the whole follow-up period, stratified by sex. CD, coeliac disease.

**Table 1** Length and weight mean z-scores on selected months for CD and no CD groups

Months	n		Length (mean z-score)			Weight (mean z-score)		
	CD	No CD	CD	No CD	Differences ( $\pm 95\%$ CI)	CD	No CD	Differences ( $\pm 95\%$ CI)
0	104	816	0.39	0.4	-0.01 (-0.21 to 0.21)	-0.22	-0.22	0.0 (-0.17 to 0.17)
1	83	616	-0.44	-0.46	-0.02 (-0.22 to 0.26)	-0.53	-0.48	-0.05 (-0.26 to 0.15)
4	88	605	-0.11	0.13	-0.22 (-0.45 to 0.01)	-0.20	-0.07	-0.13 (-0.38 to 0.10)
12	88	605	-0.02	0.26	-0.28 (-0.50 to -0.06)	-0.68	-0.32	-0.36 (-0.58 to -0.14)
24	75	516	-0.20	0.21	-0.41 (-0.65 to -0.17)	-0.36	-0.03	-0.33 (-0.57 to -0.08)

CD, coeliac disease.

0.28 SD (0.8 cm) shorter than controls ( $p=0.012$ ) and 0.36 SD (380 g) lighter ( $p=0.002$ ). At 24 months CD cases were 0.41 SD (1.47 cm) shorter than those with no CD ( $p=0.001$ ) and weighed 0.33 SD (544 g) lighter ( $p=0.10$ ).

### Growth rate by linear mixed model

Since none of the cases developed symptoms or antibodies in the first year of life, we analysed the growth of the infants in the first year, when they were free of symptoms and antibodies. The growth profile of cases and control in the first year of life fitted by smoothing splines is shown in [figure 2A](#) (weight z-score) and [figure 2B](#) (length z-score), where it may be observed that there are differences between cases and controls since the early months of life. Using a linear mixed model, children who develop CD had a significantly lower growth rate in weight z-score than those who do not develop CD ( $-0.027$  z-score/month; 95% CI  $-0.038$  to  $-0.017$ ;  $p<0.001$ ). Similarly, girls and boys with CD have lower growth rate in length/height compared with their counterparts who do not develop CD, although this difference was lower than that observed for weight ( $-0.018$  z-score/month; 95% CI  $-0.031$  to  $-0.005$ ;  $p=0.008$ ). When estimating the growth rate for the whole follow-up period (0–6 years), significant differences between the two groups were confirmed both for weight ( $-0.006$  z-score/month; 95% CI  $-0.009$  to  $-0.004$ ;  $p<0.001$ ) and length/height ( $-0.007$  z-score/month; 95% CI  $-0.010$  to  $-0.005$ ;  $p<0.001$ ).

[Figure 3A](#) shows the estimated (by linear mixed models) regression line of the growth in standardised weight of the two cohorts: both girls and boys with CD followed a lower profile

compared with no CD. Very similar profile is observed in the growth in length/height ([figure 3B](#)).

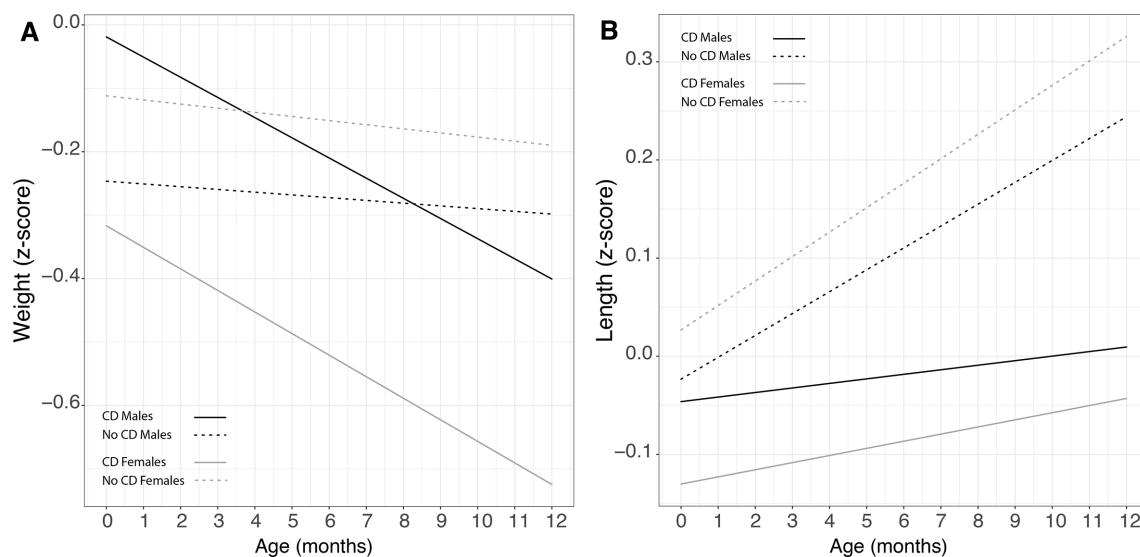
### DISCUSSION

Impaired growth, as assessed at the time of CD diagnosis, has long been recognised to be a common manifestation of CD.<sup>13 14</sup> It was recently shown that if patients with CD are identified and put on a gluten-free diet, they show no growth impairment.<sup>15</sup> In this study we investigated growth in a large prospective cohort of children at risk of CD, because they were either human leucocyte antigen (HLA) DQ2/DQ8-positive or as well as had first-degree relative affected by CD.

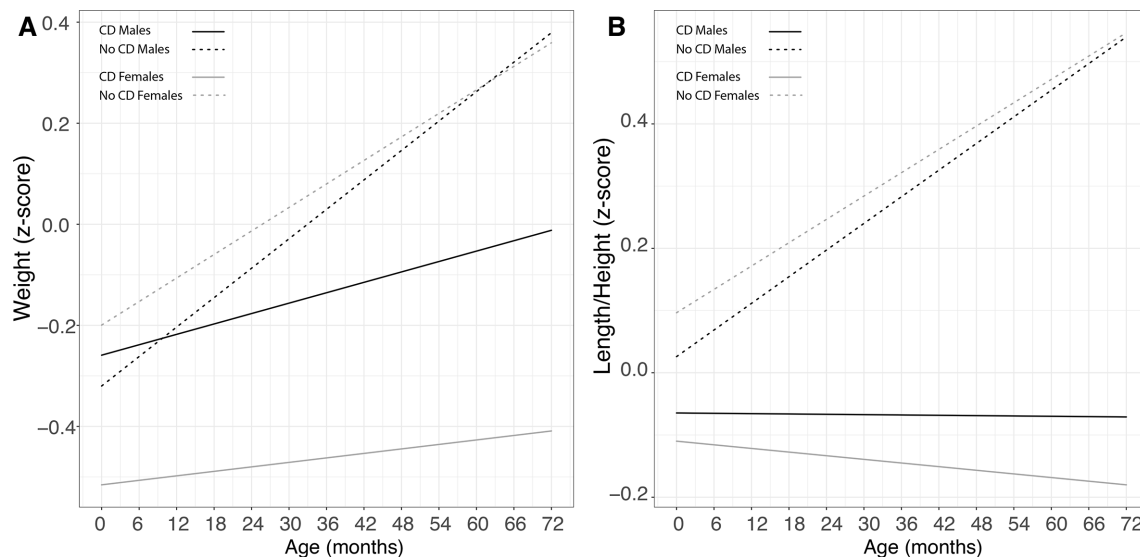
The prospective cohort study design well compensated for possible confounding variables between CD cases and children who did not develop CD by the age of 6 years (no CD controls).

We found that growth rate in weight as well as in length/height was significantly lower in children who eventually developed CD than in controls, although the average z-score never fell below  $-1$  in these cases of CD. The weight and length of cases and controls were normal at birth, but very early, the mean z-scores for weight and height differed significantly between the two groups already at 4 months. The monthly increments also in z-scores for weight and height, as estimated by the slope of the regression line, differed significantly in terms of outcome.

The differences observed were robust and consistent over the age span of 0–6 years, as shown by the slope of mixed linear regression model. The size of the differences between cases and controls was small enough to have little clinical relevance up to 4 months of age, but at 4 months boys with CD were about 0.5 cm



**Figure 2** Linear mixed model profile of weight in z-score (A) and length in z-score (B) for boys and girls during the first year of life. CD, coeliac disease.



**Figure 3** Estimated growth profile of weight in z-score (A) and length in z-score (B) during the whole follow-up period, stratified by sex. Coefficients were estimated using a linear mixed model, with time coded numerically as months from birth, gender, group and all the two-order interactions. CD, coeliac disease.

shorter than their peers with no CD and weighed about 66 g lighter. At 4 months girls with CD were 0.83 cm shorter and 258 g lighter than girls with no CD.

The differences in growth increments between the cases and controls observed in this study are based on mean values, not individuals, and the variability between individuals is too large to allow for individual differences to emerge. We then have to accept that the findings are interesting in terms of CD aetiology, but that they are unlikely to be useful clinically for prediction of CD as an isolated finding.

When growth was observed just plotting the means of raw data (figure 1), it is difficult to observe any major difference between children who develop the disease (CD) and those who do not develop the disease (no CD), since growth failure was not a relevant symptom in those who develop CD. But it is sufficient to convert the raw data into their standardised values (as should be done to estimate the ‘normality’ of the growth profile) to observe significant differences in the growth rate of the children in the two groups. Figure 2 shows the dynamic profile of growth for the two groups, by sex, in the first year of life. online supplementary figure 1 shows just the means of standardised weight and length for the two groups by sex fitted by a simple smoothing spline.

It is interesting to note that, while the standardised length of CD cases is below that of the no CD group since the early months of life for both sexes, the standardised weight of the boys who develop CD does start from birth with values close to 0 (50<sup>th</sup> centile), but at 4 months cross down the lines of the no CD group towards negative values.

Our results are consistent with retrospective studies showing that children with CD could have been identified earlier if their growth had been regularly monitored, since growth was already delayed 2 years before CD diagnosis.<sup>5</sup> Notably, delayed growth from 6 months to 8 years of age was reported in children with positive serum antitissue transglutaminase antibodies.<sup>16</sup> However, other investigators did not find abnormal growth in children with persistently elevated antibodies at the age of 4 years.<sup>7</sup> Our data confirm a recent report from Norway that showed growth retardation in children from the general population who were later diagnosed clinically with CD, well before

clinical symptoms appeared.<sup>7</sup> What is striking in our data set is that reduced growth was present not only much before antitissue transglutaminase antibodies (TGA-IgA) were detected in serum, but also before gluten was introduced in the diet.

A strength of our study is the prospective data collection from a single cohort of children from families at risk of CD, monitored longitudinally for more than 6 years with a very strict protocol. An eventual limitation could be the lack of ability to double-check the measurements taken at participating centres for both cases and controls.

It is difficult to explain such early delayed growth. Both cohorts were perfectly matched, and confounding variables could not have been related to the very distant outcome since they were well matched in the two outcome groups.<sup>11</sup> The possibility that growth may be affected before seroconversion, as suggested by previous observations, could be explained by a minor degree of enteropathy/inflammation preceding the appearance of CD-specific autoantibodies in the serum.<sup>3</sup> In this context, it is interesting that the expression of a small set of CD-associated genes, with a specific functional profile, examined in the peripheral blood monocytes of infants from 4 to 9 months, discriminates accurately children who will later develop CD from those who will not. The gene expression signature is also differentiated much before the production of TGA-IgA or the appearance of clinical signs.<sup>8</sup> If children are correctly identified and treated, there will be no impairment on the final height.<sup>15</sup>

As mentioned, our data suggest that some alterations may become manifest even before gluten introduction. Genetic variants associated with increased risk of CD could predispose to growth problems. Indeed, the CD-associated HLA haplotype has also been associated with slower growth in the first 24 months of life,<sup>17</sup> but the eventual effect of HLA haplotype could not be evaluated in our cohort since all newborns were HLA DQ-positive. Furthermore, CD-predisposing factors may be present also before gluten introduction and could contribute to growth impairment. Infections may be among these factors. However, neither infections nor any other clinical events were found to be related to the outcome in the whole cohort. We observed an increased incidence of respiratory infections in the first and second year of life in 373 infants of the Italian cohort



with an OR of 2.20 compared with those who did not.<sup>18</sup> In the present study, the small difference in the growth profile of the two cohorts did not coincide with such specific comorbidities as gastrointestinal or respiratory infections. Indeed, growth delay was a constant and regular finding throughout the study. In conclusion, we confirm that growth delay is a very early event in the natural history of CD. It even precedes gluten introduction, which suggests that infants who eventually develop CD are 'different' when they leave the protective environment of the mother. An early and careful analysis of some important factors, such as growth, can make it possible to identify, within at-risk groups, the children who will probably develop CD and to establish very early interventions. We should reinforce the opportunity to strictly monitor the growth of genetically at risk infants, since a constant deflection from the growth pathway from the first year of life onwards should prompt a 6-monthly check of the production of TGA-IgA antibodies.

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**Funding** This work was funded by the PreventCD Project (EU-FP6-2005-FOOD4B-contract no. 036383).

**Disclaimer** The funders had no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the medical ethics committees of the participating centres.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Data available through ydongre@unina.it.

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