Early growth in children with coeliac disease: a cohort study

Christian R Kahrs,[1,2] Maria C Magnus,[3,4,5] Hein Stigum,[3] Knut E A Lundin,[6,7] Ketil Størdal[1,2]

[1]Department of Pediatrics, Østfold Hospital Trust, Grålum, Norway
[2]Department of Child Health, Norwegian Institute of Public Health, Oslo, Norway
[3]Department of Non-Communicable Diseases, Norwegian Institute of Public Health, Oslo, Norway
[4]MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
[5]School of Social and Community Medicine, University of Bristol, Bristol, UK
[6]Department of Gastroenterology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[7]Centre for Immune Regulation, University of Oslo, Oslo, Norway

Correspondence to
Dr Christian R Kahrs, Department of Pediatrics, Østfold, Hospital Trust, Kalnesveien 300, Grålum 1714, Norway; ckahrs79@gmail.com

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ABSTRACT

Objectives We aimed to study growth during the first 2 years of life in children later diagnosed with coeliac disease compared with children without, in a time with changing epidemiology and improved diagnostics.

Design A prospective population-based pregnancy cohort study.

Setting The nationwide Norwegian Mother and Child Cohort Study.

Patients 58 675 children born between 2000 and 2009 with prospectively collected growth data. Coeliac disease was identified through combined data from questionnaires and the Norwegian Patient Register.

Main outcome measures The differences in height and weight at age 0, 3, 6, 8, 12, 15–18 and 24 months using internally standardised age and gender-specific z-scores. Linear regression and mixed models were used.

Results During a median follow-up of 8.6 years (range 4.6–14.2), 440 children (0.8%) were diagnosed with coeliac disease at a mean age of 4.4 years (range 1.5–8.5). Children with coeliac disease had significantly lower z-scores for height from 12 months (−0.09 standard deviation scores (SDS), 95% CI −0.18 to −0.01) and weight from 15 to 18 months of life (−0.09 SDS, 95% CI −0.18 to −0.01) compared with cohort controls. The longitudinal analysis from 0 to 24 months yielded a significant reduction in height z-score per year (−0.07 SDS, 95% CI −0.13 to −0.01) but not for weight among children with coeliac disease. Excluding children diagnosed before age 2 years gave similar results.

Conclusions This study indicates that growth retardation in children later diagnosed with coeliac disease commonly starts at 12 months of age, and precedes clinical symptoms that usually bring the suspicion of diagnosis.

What is already known on this topic?

- Impaired growth is common at diagnosis of coeliac disease.
- Growth faltering may be an early sign, but has mainly been studied for a limited time before diagnosis.

What this study adds?

- Growth retardation in children later diagnosed with coeliac disease commonly starts before the age of 2.
- Growth retardation may precede clinical symptoms that usually bring the suspicion of a diagnosis of coeliac disease.

INTRODUCTION

Coeliac disease is an immune-mediated disorder affecting 1%–3% of children in Nordic countries.[1 2] The main presentations of coeliac disease are now recurrent abdominal pain and growth retardation,[3] but screening of school children without or with mild symptoms highlights that a large proportion remains undetected.[4]

Impaired growth is a common and early manifestation of 'classic' coeliac disease in children.[5] Although length and weight are below the mean of age in children with coeliac disease, the majority do not have a growth disturbance leading to the diagnosis.[6] Screening-detected children, who may be phenotypically different from those clinically diagnosed, have also been reported to be lighter, shorter and have a lower body mass index.[7] These features may occur independent of gastrointestinal symptoms and anaemia.[8 9]

Most prior studies have reported growth measures at the time of coeliac disease diagnosis, but few studies have assessed growth longitudinally. One screening study found normal growth by age 4 years in children with persistently elevated tissue transglutaminase antibodies (tTGA),[10] whereas another reported reduced growth trajectory from 6 months until 6 years of age in tTGA-positive children at 6 years of age.[11] A study based on clinical diagnosis showed that growth may be affected several years before diagnosis,[12] but still little is known about when this process starts.

We aimed to study whether growth in the first 2 years of life differs between children diagnosed with coeliac disease and children without the diagnosis in a large, prospective birth cohort.

METHODS

Study population

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[13 14] The nationwide cohort, born in 1999–2009, now includes more than 112 000 children. The current study is based on version VIII of the quality-assured data files released for research in February 2014, comprising information from questionnaires administered on recruitment at 18 gestational weeks, and when the child was 6, 18 and 36 months of age. Children with missing

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growth data at birth or 15–18 months were excluded. Information from the MoBa follow-up questionnaires was subsequently linked to the Medical Birth Registry of Norway (MBR) and the Norwegian Patient Register (NPR). MoBa has obtained a licence from the Norwegian Data Inspectorate, and the current study was approved by the Regional Committee for Medical Research Ethics of South-East Norway.

Growth measurements

Birth weight and length were collected from the MBR. The child's weight and length at 3, 6, 8, 12, 15–18 and 24 months were recorded by public health nurses according to guidelines from the Norwegian Directorate of Health, and transferred to the MoBa questionnaires by participating mothers.[15] Anthropometric measurements were transformed to age-specific and sex-specific internally standardised z-scores. We decided to use internally standardised z-scores instead of externally standardised z-scores due to the large sample size of the MoBa cohort.

In our population both height and weight distributions were quite close to normality, and we therefore used the simple method of calculating z-scores without fitting for skewness.[16 17]

Outcome

We defined the main outcome coeliac disease as at least two registrations of the International Classification of Diseases-10 code K90.0 in the NPR by 31 December 2013 or coeliac disease reported by parental questionnaires administered at child's age 7–8 years, and validated as shown elsewhere.[18] For the children with coeliac disease participating in the validation study, additional information on preceding symptoms, age at diagnosis and diagnostic methods was available.[19]

Covariates

Based on previous literature we included covariates that may influence both postnatal growth and risk of coeliac disease (confounders), covariates that may influence postnatal growth or risk of coeliac disease (predictors), and covariates that may have influenced selection to the present study (see directed acyclic graph, online supplementary figure 1).[18 20 21] Sex and preterm birth were obtained from the MBR. Data on the child's infection frequency up to age 18 months, maternal educational level, smoking in pregnancy, breast feeding and parental growth parameters were obtained from the questionnaires. Maternal coeliac disease status was obtained from questionnaires and linkage to NPR. For categorisation of covariates, see table 1.

Statistical methods

To assess whether growth characteristics were different between the case and control groups, two different types of analyses were performed. First, we performed cross-sectional analyses to examine associations between growth parameters and development of coeliac disease at different time points using linear regression models: (1) a crude model, (2) adjusting for baseline z-scores for height and weight, and (3) the main multivariable model (table 2).

Second, to longitudinally assess associations between coeliac disease and growth, we used linear mixed models adjusted for the same covariates as in model 3. These models take the correlations between repeated measurements within the same subject into account. Random intercepts were fitted and random slopes included. The plots of z-scores across age appeared to be linear, and addition of higher degree age terms in the model did not provide a better fit to the data. The unstructured model provided the smallest goodness-of-fit indices (akaike information criterions (AICs)) and was therefore applied.

In preplanned sensitivity analyses we restricted analyses to children with diagnosis or symptoms of coeliac disease after 2 years to avoid any influence of early-onset coeliac disease. To account for siblingships, we used cluster variance estimations. Approximately 10%–20% had missing covariate or growth data, and missing data were therefore imputed using chained equations, generating a total of 20 imputed data sets. Finally, to test whether our case definition of coeliac disease influenced the findings, we restricted our analyses to children with a parent-confirmed coeliac disease diagnosis. A 95% CI excluding 1.00 was considered statistically significant. The analysis was conducted using SAS V.9.4 and Stata V.14.

RESULTS

For our primary analysis, sufficient follow-up data were available for 58 235 cohort controls and 440 children (0.7%) with coeliac disease (see flow chart, figure 1). The mean age at the end of follow-up was 8.6 years (range 4.6–14.2), with background characteristics presented in table 1. Maternal coeliac disease was more common among cases than controls, and 61% of the cases were girls. Maternal education and gestational age were higher whereas parity and the proportion of smokers were lower among children included in the present study as compared with those not included. Furthermore, included children were longer and heavier at birth and had a slightly higher prevalence of coeliac disease (0.75% vs 0.61%) as compared with excluded children. The distribution of absolute growth parameters is presented in online supplementary table 1.

Height

In the cross-sectional analysis height growth differed in the first year of life between coeliac disease children and cohort controls at the end of follow-up and was significantly reduced from age 12 months (−0.09 standard deviation scores (SDS), 95% CI −0.18 to −0.01; table 2 and figure 2).

The reduction accelerated between 12 and 24 months corresponding to a difference of 0.8 cm at 24 months of age.

The longitudinal analysis for the period 0–12 months yielded a non-significant reduction in height z-score for children with coeliac disease, whereas the period 0–24 months yielded a significant reduction (−0.07 SDS per year, 95% CI −0.13 to −0.01; figure 2), as compared with children without the diagnosis.

Weight

Children later diagnosed with coeliac disease were non-significantly lighter already at birth. The difference was significant from 15 to 18 months (−0.09 SDS, 95% CI −0.18 to −0.01; table 2 and figure 2) and then gradually increased, corresponding to a difference between cases and cohort controls of approximately 250 g at 24 months of age.

The longitudinal analysis from 0 to 12 months yielded no significant differences for weight among children with coeliac disease versus controls at the end of follow-up, with similar non-significant differences from 0 to 24 months of age (−0.01 SDS, 95% CI −0.08 to 0.05).

Sensitivity analyses

Among the subset with additional details available from the validation study,[18] the mean age at coeliac disease diagnosis was 4.4 years (SD 2.4), and the mean time from start of symptoms

Table 1 Background characteristics of the study cohort

	Included children* n=58 675		Excluded children† n=54 029
	Coeliac disease n=440	No coeliac disease n=58 235	
Maternal age (mean (SD))			
	30.2 (4.2)	30.3 (4.4)	29.9 (4.9)
Maternal parity (n (%))			
0	206 (46.8)	27 286 (46.9)	21 924 (41.1)
1	160 (36.4)	20 178 (34.7)	19 755 (37.0)
2+	74 (16.8)	10 771 (18.5)	11 651 (21.8)
Maternal education (n (%))‡			
High school or less than high school	138 (31.5)	19 842 (34.2)	18 371 (42.4)
Up to 4 years of college	185 (42.2)	24 860 (42.8)	15 758 (36.3)
More than 4 years of college	115 (26.3)	13 320 (23.0)	9241 (21.3)
Maternal length (mean (SD))			
	168.1 (6.2)	168.2 (5.9)	167.9 (6.1)
Maternal prepregnancy BMI (n (%))			
Underweight (<18.5)	20 (4.6)	1626 (2.9)	1485 (3.5)
Normal weight (18.5–24.9)	290 (66.8)	37 598 (66.0)	27 226 (64.6)
Overweight/obese (≥25)	124 (28.6)	17 736 (31.1)	13 456 (31.9)
Paternal length (mean (SD))			
	181.7 (5.8)	181.6 (6.4)	181.4 (6.5)
Paternal BMI (n (%))			
Underweight (<18.5)	2 (0.5)	110 (0.2)	98 (0.2)
Normal weight (18.5–24.9)	193 (45.7)	25 198 (45.1)	18 170 (44.2)
Overweight/obese (≥25)	227 (53.8)	30 536 (54.7)	22 847 (55.6)
Smoking during pregnancy (n (%))			
Yes	23 (5.2)	4088 (7.1)	4501 (10.4)
Maternal coeliac disease (n (%))§			
Yes	43 (9.8)	424 (0.7)	415 (0.8)
Gestational age in weeks (categorical)			
<37	23 (5.3)	2273 (3.9)	5319 (10.0)
Child gender (n (%))			
Female	270 (61.4)	28 321 (48.6)	25 874 (48.7)
Duration of breast feeding (n (%))			
<6 months	57 (13.2)	9277 (16.4)	3579 (22.0)
6–12 months	170 (39.5)	24 979 (44.2)	7000 (43.1)
≥12 months	203 (47.2)	22 276 (39.4)	5667 (34.9)
Infection frequency 0–18 months (n (%))			
0–4 episodes	104 (24.3)	14 151 (25.2)	4046 (25.4)
5–6 episodes	73 (17.1)	11 494 (20.5)	3091 (19.4)
7–9 episodes	110 (25.7)	14 538 (25.9)	4026 (25.3)
≥10 episodes	141 (32.9)	16 005 (28.5)	4764 (29.9)
Attained age end 2013 (mean (SD))			
	8.9 (2.1)	8.6 (2.2)	8.5 (2.2)
Birth weight in kg (SD)			
	3.54 (0.53)	3.62 (0.53)	3.50 (0.64)
Birth length in cm (SD)			
	50.2 (2.2)	50.5 (2.2)	50.1 (2.5)

*Data were available in >95% of the included children.
†Data were available in 30%–99% of the excluded children. Prevalence of coeliac disease among excluded participants: 326/54 029 (0.6 %).
‡Maternal education level at time of pregnancy, categorised into ≤12 years of education, 13–15 and ≥16 years. Percentages may not total 100% because of rounding.
§Identified through pregnancy questionnaires and the Norwegian Patient Registry.
BMI, body mass index.

recorded by the parents until diagnosis was 6 months (SD 0.8) (see online supplementary figure 2A,B).

Excluding children with debut of symptoms or diagnosed before 2 years of age yielded largely similar results as our main analysis (see online supplementary table 2). Restricting our analysis to parent-confirmed diagnosis, we found largely unchanged results (data not shown). The results from the multiple imputation and complete case analysis were similar (see online supplementary

Table 2 Association between coeliac disease and anthropometric z-scores at different time points from birth to 24 months of age (n=440 cases, 58 235 cohort controls)

Anthropometric measurement	Model 1* (coefficient, 95% CI)	Model 2† (coefficient, 95% CI)	Model 3‡ (coefficient, 95% CI)
Length			
Birth	−0.06 (−0.15 to 0.04)	−0.06 (−0.15 to 0.04)	−0.02 (−0.11 to 0.06)
3 months	−0.08 (−0.18 to 0.02)	−0.06 (−0.13 to 0.01)	−0.07 (−0.14 to 0.00)
6 months	−0.10 (−0.20 to −0.01)	−0.07 (−0.15 to 0.01)	−0.08 (−0.16 to −0.00)
8 months	−0.12 (−0.22 to −0.02)	−0.07 (−0.15 to 0.01)	−0.07 (−0.15 to 0.02)
12 months	−0.12 (−0.21 to −0.02)	−0.08 (−0.17 to 0.00)	−0.09 (−0.18 to −0.01)
15–18 months	−0.12 (−0.22 to −0.03)	−0.10 (−0.19 to −0.02)	−0.11 (−0.19 to −0.03)
24 months	−0.26 (−0.39 to −0.12)	−0.23 (−0.35 to −0.11)	−0.24 (−0.36 to −0.12)
Weight			
Birth	−0.12 (−0.21 to −0.03)	−0.12 (−0.21 to −0.03)	−0.07 (−0.15 to 0.02)
3 months	−0.08 (−0.18 to 0.02)	−0.03 (−0.11 to 0.05)	−0.03 (−0.11 to 0.05)
6 months	−0.11 (−0.21 to −0.02)	−0.06 (−0.15 to 0.03)	−0.05 (−0.14 to 0.04)
8 months	−0.11 (−0.21 to −0.01)	−0.05 (−0.14 to 0.04)	−0.02 (−0.11 to 0.07)
12 months	−0.15 (−0.24 to −0.05)	−0.10 (−0.19 to −0.01)	−0.07 (−0.16 to 0.02)
15–18 months	−0.15 (−0.24 to −0.06)	−0.11 (−0.20 to −0.02)	−0.09 (−0.18 to −0.00)
24 months	−0.21 (−0.35 to −0.08)	−0.17 (−0.29 to −0.04)	−0.16 (−0.29 to −0.03)

Coefficients are based on linear regression models and reflect between group differences in mean height and weight relative to reference group.
*Crude model unadjusted.
†Baseline model adjusted for z-score at birth. Data were available in ≥90% of the children except in 55% at 24 months.
‡Multivariable model adjusted for z-score at birth, maternal coeliac disease, maternal education, maternal smoking in pregnancy, birth weight, preterm birth, duration of breast feeding and childhood infections 0–18 months.

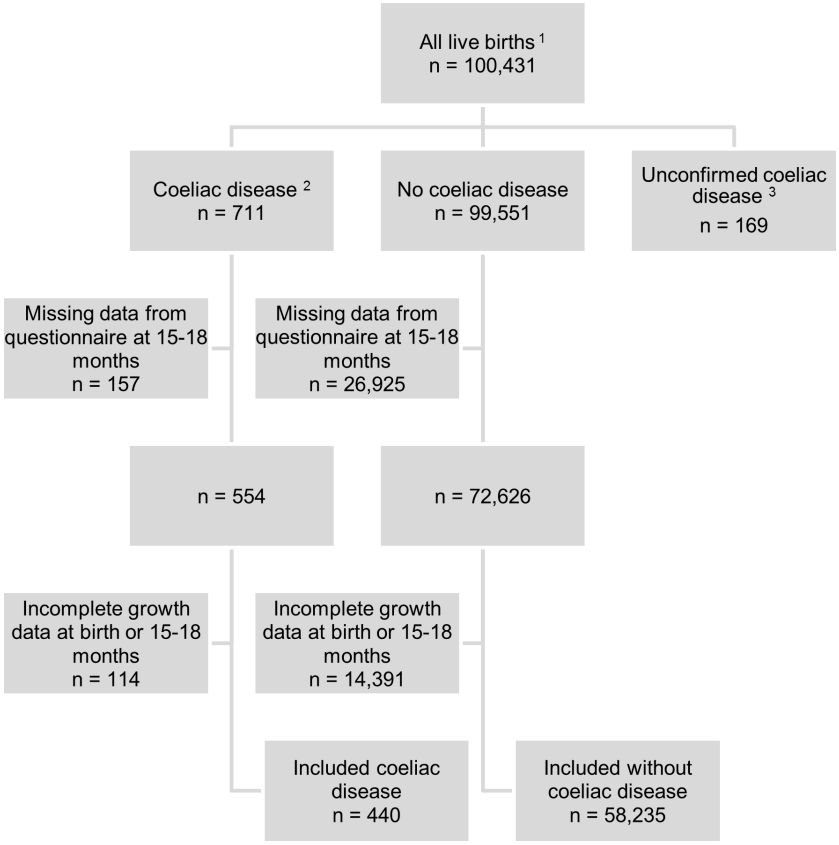

Figure 1 Flow chart of study population. [1]Children whose parent returned questionnaire at recruitment (week 18 of pregnancy). Multiparous were excluded. [2]Coeliac disease defined as at least two registrations of the International Classification of Diseases-10 code K90.0 in the Norwegian Patient Registry (NPR) by 31 December 2013 or coeliac disease confirmed through parental questionnaires. [3]102 children with a single registration of coeliac disease in the NPR and without questionnaire confirmation were regarded to have unconfirmed coeliac disease and excluded from the analyses. 67 children with a possible coeliac disease diagnosis could neither be confirmed nor rejected in the validation survey, and these children were also excluded from the analyses.

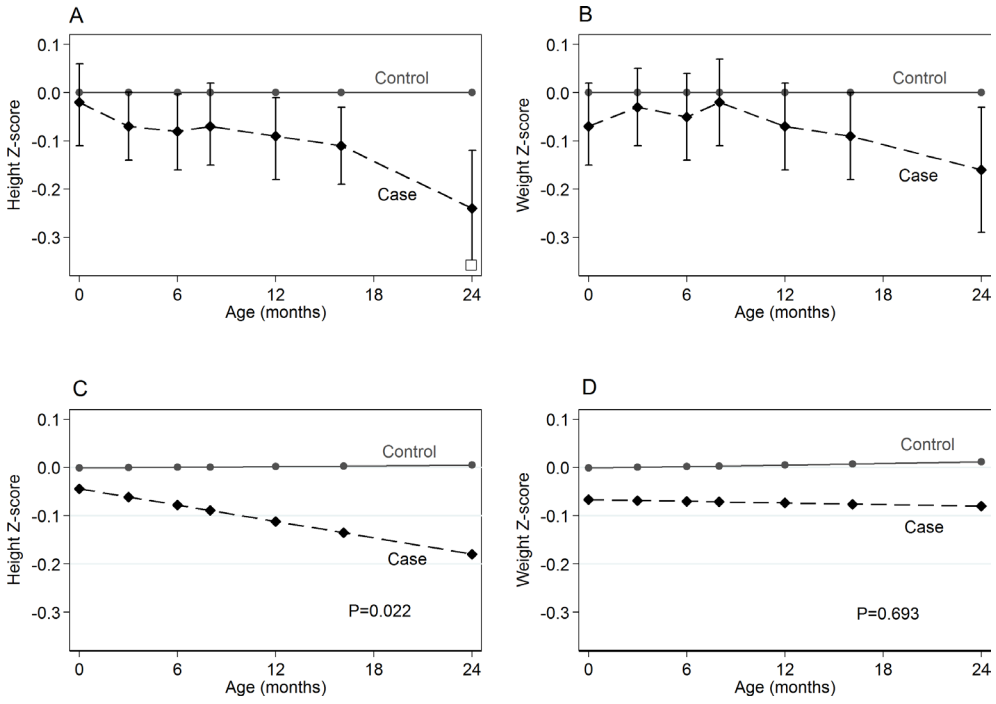

Figure 2 (A,B) Height and weight z-scores for children with coeliac disease and controls from birth until 24 months based on a linear regression model. (C,D) Height and weight z-scores for children with coeliac disease and controls from birth until 24 months based on a linear mixed model. (A,B) Values (adjusted betas) are based on the multivariable linear regression model (see table 2) and reflect between-group differences (with 95% CIs) in mean height and weight. (C,D) Longitudinal growth differences between children with coeliac disease relative to controls. Estimated regression lines derived from linear mixed models analysis reflect differences in height (C) and weight (D) z-scores from birth until 24 months of age in children with coeliac disease relative to controls. (C) Significant difference in height over time (p=0.022). Significant difference in height z-score (−0.18) at 24 months of age (p=0.002). (D) No difference in weight over time (p=0.693). No difference in weight at 24 months of age.

table 3). Using robust cluster variance estimations and adjustment for predisposing human leukocyte antigen (HLA) types yielded minor changes in the main estimates.

DISCUSSION

In this large prospective birth cohort, children later diagnosed with coeliac disease were shorter as early as 12 months of age compared with those without diagnosis at the end of follow-up. The differences in absolute numbers were small but increased the second year of life. The results were largely consistent in sensitivity analysis excluding children with symptoms from before 2 years of age.

Strengths of the current study include the population-based design and the prospective data collection with details on potential confounding factors, which allowed for adjusted estimates. The large sample size of the cohort provided growth data for accurate estimation of internally standardised z-scores. The combination of questionnaire data and linkage to national health registers should ensure a high level of case ascertainment. However, as in any observational study, confounding from unmeasured factors may be present. The prevalence of undiagnosed coeliac disease in the present cohort should not exceed 1%–2%,[2] which could have biased our results towards the null.

We cannot exclude a potential selection bias due to the initial participation rate or due to loss to follow-up. The observed prevalence of clinical coeliac disease in the MoBa cohort is similar to findings from two other Norwegian studies.[3 22] Still, it is likely that some children will be diagnosed with coeliac disease when they are older. Of greater concern is the exclusion of children lacking growth information. To reduce this potential for bias, we adjusted our analyses for the covariates differing among included and excluded (see online supplementary figure 2). Using maternal report of the child's anthropometric measurements might have resulted in information bias. By requesting the mothers to transfer data from the child's health records, we attempted to minimise misclassification. The slight variation in exact age at anthropometric measurements (see online supplementary table 4) was adjusted for by analysing growth measures as age-specific and sex-specific z-scores.

To the best of our knowledge, this is the first cohort study to compare growth from birth in children later clinically diagnosed with coeliac disease and children without. The wide range of designs and outcome definitions used in previous studies makes comparisons difficult. Our findings are consistent with a previous retrospective longitudinal study from Finland, reporting that growth was affected in most children several years before clinical diagnosis.[12] However, the present study reports growth from birth and not in relation to the time of diagnosis.

The results from screening studies have been somewhat inconsistent. Our results are in line with a recent population-based cohort study reporting that seropositive children detected by screening at the age of 6 tended to be shorter and weigh less at 6 months than seronegative children, most prominent in children with tTGA levels ≥10 times the upper limit of normal.[11] In contrast, a birth cohort with increased genetic risk for coeliac disease performing annual screening found normal growth at age 4 in children with persistently elevated tTGA.[10] However, since the time from seroconversion to diagnosis will differ between screening studies and studies based on clinical diagnosis, and also between studies with longitudinal screening and studies with cross-sectional screening, the results are not directly comparable.

The children with coeliac disease in our study tended to be born earlier, with lower birth weight (tables 1 and 2). Some prior studies have found a positive association between coeliac disease and being born small for gestational age, but data are conflicting.[23–26] This association may also be due to surveillance bias because children born small and preterm may be more likely to be investigated, including diagnostic work-up for coeliac disease.

The findings of our study have a number of potential implications. First, our results indicate that overall growth in height may be affected as early as in the first year of life. Second, as symptoms started at a mean of 4 years, this suggests that growth impairment commonly starts before other symptoms. Third, as low-grade enteropathy may occur without seroconversion in adult patients,[27] we speculate that growth may be impaired earlier than actual seroconversion. A limitation of the current study is that the cohort was not prospectively screened, but the fact that seroconversion usually occurs after 2 years of age may support this hypothesis.[28]

Our findings may be explained by a small proportion of children with coeliac disease with early diagnosis and severe growth reduction. However, we found largely similar results when restricting our analysis to children with debut of symptoms after 2 years of age. Therefore, we find it more likely that subtle changes in growth, difficult to identify without other symptoms, occur early and commonly in children with coeliac disease.[4] Although the mechanisms and nature of catch-up growth are yet not fully understood, unrecognised coeliac disease with reduced growth in childhood might cause reduced adult height.[29 30] This may suggest that growth may improve by early detection and treatment of coeliac disease, and calls for new diagnostic strategies enabling earlier detection of coeliac disease.

Growth retardation in coeliac disease may be explained by malnutrition due to villous atrophy, but the evidence is scant.[31] Other proposed mechanisms are systemic inflammation, disturbance in the growth hormone axis and increased prevalence of antipituitary antibodies.[32 33] A Finnish study found that children with only poor growth were markedly different from those with other concomitant symptoms, suggesting different pathogenic mechanisms.[34]

Genetic variants associated with increased risk of coeliac disease could potentially predispose to reduced growth. In children with HLA-conferred risk for type 1 diabetes, the high-risk genotype HLA DQ2/8 has been associated with higher birth weight but also slower growth in the first 24 months of life.[35 36] Adjustment for predisposing genotype, which was available for a subset of the participants, yielded only minor changes in our estimates.

Maternal coeliac disease is known to be associated with increased risk of offspring coeliac disease, and undiagnosed maternal coeliac disease has been associated with increased risk of being born preterm or small for gestational age.[37] However, our results on postnatal growth were robust against adjustment for baseline z-scores and for maternal coeliac disease including those diagnosed after pregnancy.

Finally, frequent infections could impair growth and predispose to coeliac disease,[18 38] but adjustment for infections does not suggest that this may explain our findings.

CONCLUSIONS

In conclusion, we found that children with coeliac disease are shorter already at 12 months of age and weigh less from 15 to 18 months. However, we urge caution in the interpretation as selection bias might have influenced our results. Longitudinal studies of growth from birth and repeated screening for coeliac disease are needed to further elucidate the nature and underlying mechanisms of growth restriction.

Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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Contributors CRK conceptualised and designed the study, performed the data analyses and wrote the initial manuscript. MCM contributed to the design of the study, assisted with the statistical analyses and interpretation of the data, and critically revised the manuscript. HS assisted with the statistical analyses and interpretation of the data, and critically revised the manuscript. KEAL contributed to interpretation of the data and critically revised the manuscript. KS is the principal investigator and contributed to the design of the study, assisted with the statistical analyses and interpretation of the data, and critically revised the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

Patient consent This was a cohort study were only women who consented to participate (written informed consent) were recruited.

Ethics approval The current study was approved by the Regional Committee for Medical Research Ethics of South-East Norway.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement It is possible for everyone to apply for access to MoBa data. There are no additional unpublished data from the current study. Our data will be available for editor/reviewer upon request.

REFERENCES

1 Mäki M, Mustalahti K, Kokkonen J, *et al*. Prevalence of Celiac disease among children in Finland. *N Engl J Med* 2003;348:2517–24.
2 Myléus A, Ivarsson A, Webb C, *et al*. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr* 2009;49:170–6.
3 Beitnes AR, Vikskjold FB, Jóhannesdóttir GB, *et al*. Symptoms and mucosal changes stable during rapid increase of Pediatric Celiac Disease in Norway. *J Pediatr Gastroenterol Nutr* 2017;64:586–91.
4 Lebwohl B, Ludvigsson JF, Green PH. Celiac disease and non-celiac gluten sensitivity. *BMJ* 2015;351:h4347.
5 Patwari AK, Kapur G, Satyanarayana L, *et al*. Catch-up growth in children with late-diagnosed coeliac disease. *Br J Nutr* 2005;94:437–42.
6 Kivelä L, Kaukinen K, Lähdeaho ML, *et al*. Presentation of celiac disease in finnish children is no longer changing: a 50-Year Perspective. *J Pediatr* 2015;167:1109–15.
7 van der Pals M, Myléus A, Norström F, *et al*. Body mass index is not a reliable tool in predicting celiac disease in children. *BMC Pediatr* 2014;14:165.
8 Bingley PJ, Williams AJ, Norcross AJ, *et al*. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. *BMJ* 2004;328:322–3.
9 Mubarak A, Spierings E, Wolters VM, *et al*. Children with celiac disease and high tTGA are genetically and phenotypically different. *World J Gastroenterol* 2013;19:7114–20.
10 Agardh D, Lee HS, Kurppa K, *et al*. Clinical features of celiac disease: a prospective birth cohort. *Pediatrics* 2015;135:627–34.
11 Jansen MA, Kiefte-de Jong JC, Gaillard R, *et al*. Growth trajectories and bone mineral density in anti-tissue transglutaminase antibody-positive children: the Generation R Study. *Clin Gastroenterol Hepatol* 2015;13:913–20.
12 Saari A, Harju S, Mäkitie O, *et al*. Systematic growth monitoring for the early detection of celiac disease in children. *JAMA Pediatr* 2015;169:e1525.
13 Nilsen RM, Vollset SE, Gjessing HK, *et al*. Self-selection and Bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;23:597–608.
14 Magnus P, Birke C, Vejrup K, *et al*. Cohort profile update: The Norwegian Mother and child cohort study (MoBa). *Int J Epidemiol* 2016;45:382–8.
15 Norwegian Directorate of Health (2010). Nasjonale faglige retningslinjer for veiing og måling i helsestasjons- og skolehelsetjenesten (In English: national guidelines for

weighing and measurements in well-baby clinics and school health services. https://helsedirektoratet.no/retningslinjer/nasjonal-faglig-retningslinje-for-veiing-og-maling-i-helsestasjons-og-skolehelsetjenesten (accessed 9 Oct 2016).
16 World Health Organization. *PhysicalStatus: The Use and Interpretation of Anthropometry. Report of a WHOExpert Committee. Technical Report Series No. 854*. . Geneva: WHO, 1995:854. 1–452. http://www.who.int/nutgrowthdb/about/introduction/en/index4.html
17 Cole TJ. Fitting smoothed centile curves to reference data (with discussion). *J R Stat Soc* 1988;151:385–418.
18 Mårild K, Kahrs CR, Tapia G, *et al*. Infections and risk of celiac disease in childhood: a prospective nationwide cohort study. *Am J Gastroenterol* 2015;110:1475–84.
19 Husby S, Koletzko S, Korponay-Szabó IR, *et al*. ESPGHAN Working Group on Coeliac Disease DiagnosisESPGHAN Gastroenterology CommitteeEuropean Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–60.
20 Mårild K, Ludvigsson JF, Størdal K. Current evidence on whether perinatal risk factors influence coeliac disease is circumstantial. *Acta Paediatr* 2016;105:366–75.
21 Hancock C, Bettiol S, Smith L. Socioeconomic variation in height: analysis of National Child Measurement Programme data for England. *Arch Dis Child* 2016;101:422–6.
22 Størdal K, Bakken IJ, Surén P, *et al*. Epidemiology of coeliac disease and comorbidity in Norwegian children. *J Pediatr Gastroenterol Nutr* 2013;57:467–71.
23 Wingren CJ, Agardh D, Merlo J. Revisiting the risk of celiac disease in children born small for gestational age: a sibling design perspective. *Scand J Gastroenterol* 2012;47:632–9.
24 Adlercreutz EH, Wingren CJ, Vincente RP, *et al*. Perinatal risk factors increase the risk of being affected by both type 1 diabetes and coeliac disease. *Acta Paediatr* 2015;104:178–84.
25 Canova C, Zabeo V, Pitter G, *et al*. Association of maternal education, early infections, and antibiotic use with celiac disease: a population-based birth cohort study in northeastern Italy. *Am J Epidemiol* 2014;180:76–85.
26 Emilsson L, Magnus MC, Størdal K. Perinatal risk factors for development of celiac disease in children, based on the prospective Norwegian Mother and Child Cohort Study. *Clin Gastroenterol Hepatol* 2015;13:921–7.
27 Salmi TT, Collin P, Korponay-Szabó IR, *et al*. Endomysial antibody-negative coeliac disease: clinical characteristics and intestinal autoantibody deposits. *Gut* 2006;55:1746–53.
28 Vriezinga SL, Auricchio R, Bravi E, *et al*. Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 2014;371:1304–15.
29 Weiss B, Skourikhin Y, Modan-Moses D, *et al*. Is adult height of patients with celiac disease influenced by delayed diagnosis? *Am J Gastroenterol* 2008;103:1770–4.
30 Pärnänen A, Kaukinen K, Helakorpi S, *et al*. Symptom-detected and screen-detected celiac disease and adult height: a large cohort study. *Eur J Gastroenterol Hepatol* 2012;24:1066–70.
31 Holtmeier W, Caspary WF. Celiac disease. *Orphanet J Rare Dis* 2006;1:3.
32 Delvecchio M, De Bellis A, Francavilla R, *et al*. Anti-pituitary antibodies in children with newly diagnosed celiac disease: a novel finding contributing to linear-growth impairment. *Am J Gastroenterol* 2010;105:691–6.
33 Street ME, Volta C, Ziveri MA, *et al*. Changes and relationships of IGFS and IGFBPS and cytokines in coeliac disease at diagnosis and on gluten-free diet. *Clin Endocrinol* 2008;68:22–8.
34 Nurminen S, Kivelä L, Taavela J, *et al*. Factors associated with growth disturbance at celiac disease diagnosis in children: a retrospective cohort study. *BMC Gastroenterol* 2015;15:125.
35 Peet A, Hämäläinen AM, Kool P, *et al*. Early postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes. *Diabetes Metab Res Rev* 2014;30:60–8.
36 Larsson HE, Lynch K, Lernmark B, *et al*. Diabetes-associated HLA genotypes affect birthweight in the general population. *Diabetologia* 2005;48:1484–91.
37 Ludvigsson JF, Montgomery SM, Ekbom A. Celiac disease and risk of adverse fetal outcome: a population-based cohort study. *Gastroenterology* 2005;129:454–63.
38 Stephensen CB. Burden of infection on growth failure. *J Nutr* 1999;129:534S–8.

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Christian R Kahrs, Maria C Magnus, Hein Stigum, Knut E A Lundin and Ketil Størdal

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