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Five-year follow-up of new cases after a coeliac disease mass screening

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2021-322755>).

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Received 29 June 2021

Accepted 28 November 2021

Published Online First

17 December 2021

ABSTRACT

Objective We previously performed a population-based mass screening of coeliac disease in children aged 12 years in two birth cohorts resulting in 296 seropositive children, of whom 242 were diagnosed with coeliac disease after duodenal biopsies. In this follow-up study, we wanted to identify new cases in the screening population that tested negative—either converting from potential coeliac disease (seropositive but normal duodenal mucosa) or converting from seronegative at screening to diagnosed coeliac disease.

Methods All seropositive children were invited to a follow-up appointment 5 years after the screening with renewed serological testing and recommended endoscopic investigation if seropositive. Seronegative children in the screening study (n=12 353) were linked to the National Swedish Childhood Coeliac Disease Register to find cases diagnosed in healthcare during the same period.

Results In total, 230 (77%) came to the follow-up appointment, including 34 of 39 with potential coeliac disease. Of these, 11 (32%) had converted to coeliac disease. One new case was found in the National Swedish Childhood Coeliac Disease Register who received the diagnosis through routine screening in children with type 1 diabetes.

Conclusions There is a high risk of conversion to coeliac disease among those with potential disease. However, a negative screening test was associated with a very low risk for a clinical diagnosis within a follow-up period of 5 years.

INTRODUCTION

Coeliac disease is an immune-mediated enteropathy characterised by inflammatory lesions in the small intestine triggered by dietary gluten in genetically susceptible individuals.¹ In children, the disease is diagnosed through verification of the enteropathy by a small intestinal biopsy or repeated serology if the criteria for the non-biopsy approach are fulfilled. It is well known that coeliac disease can cause gastrointestinal symptoms, growth retardation and anaemia. However, symptoms can be very vague and challenging to recognise in clinical practice.¹ From screening studies, we know that the disease is highly underdiagnosed in both children and adults.^{2–6} We have previously shown that active case findings extended to the general population would be ineffective and only population mass screening can identify most coeliac disease cases.⁷

What is already known on this topic?

- ⇒ In a clinical context, there is a high risk of developing coeliac disease in children who have tested seropositive but who have normal mucosal architecture.
- ⇒ Mass screening is needed to identify most coeliac disease cases in children.

What this study adds?

- ⇒ In a screening context, potential coeliac disease implies a high risk of conversion to disease with enteropathy within 5 years from a screening and needs to be followed up.
- ⇒ The risk of receiving a clinical diagnosis within 5 years from a screening is very low.
- ⇒ A possible repeated screening can wait longer than 5 years.

Undiagnosed and untreated coeliac disease, even in asymptomatic cases, can have negative health consequences in the long run related to malabsorption and increased risk of intestinal malignancies.^{8–10} However, the natural history of coeliac disease is not completely understood.¹¹ Repeated screening of risk groups, that is, individuals with type 1 diabetes, Down syndrome, Turner syndrome or having a first-degree relative with coeliac disease, are recommended.¹ An unanswered question is if a single screening event in the general population is enough or whether a possible mass screening must be repeated because coeliac disease can develop anytime during the lifespan.¹²

In 2005–2006 and 2009–2010, we performed a school-based coeliac disease mass screening of children aged 12 years.^{6 13} We found a coeliac disease prevalence of 29/1000 and 22/1000, respectively, with two-thirds undiagnosed prior to the screening in both phases. Additionally, we identified a proportion of children with potential coeliac disease in both birth cohorts. Potential coeliac disease refers to a positive serological test but with normal duodenal mucosal architecture on small intestinal biopsy, and it is generally not treated with a gluten-free diet if asymptomatic.¹

The aim of this study was to identify new cases of coeliac disease in the screening population during a 5-year follow-up period, including both cases that



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To cite: Sandström O, Norström F, Carlsson A, et al. *Arch Dis Child* 2022;**107**:596–600.

converted from potential coeliac disease to coeliac disease and clinically diagnosed cases among children who were seronegative at the time of the screening.

METHOD

Overall study design

We conducted a 5-year follow-up after a population-based mass screening in two birth cohorts of children. We followed two groups with different approaches: (1) children with positive serology in the screening were invited to a follow-up appointment at the paediatric clinic and (2) the group of children with negative (normal) serology were linked to the National Swedish Childhood Coeliac Disease Register to identify any new cases of coeliac disease diagnosis.

Information on the preceding screening study

Details of the screening study Exploring the Iceberg of Coeliacs in Sweden (ETICS) have been previously published.^{6,13,14} In total, we invited 18 325 children aged 12 years with 13 279 consenting to participate, including 100 children with coeliac disease diagnosed

prior to the study. Levels of antitissue transglutaminase IgA and IgG antibodies (anti-TG2-IgA and IgG) were measured by ELISA (Celikey Phadia, Freiburg, Germany). The recommended cut-off for the test was 5 U/mL, but we used a reduced level to increase sensitivity. Positive serology was defined as anti-TG2-IgA > 4 U/mL, or intermediate levels of anti-TG2 IgA (2–4 U/mL) in combination with endomysial antibody (EMA) positivity of 1:5 or greater. Blood samples were obtained from 12 632 children, whereof 296 tested positive and were recommended to undergo small intestinal biopsies. Biopsies were evaluated by local pathologists, and an expert pathologist re-evaluated all specimens blinded to the results of the local pathologists' assessments.⁶

In the first screening phase (2005–2006), 182 children accepted a small intestinal biopsy resulting in 153 new cases of coeliac disease. In the second screening phase (2009–2010), 99 children accepted intestinal biopsy with 89 new cases. Children with a biopsy showing normal histopathology without symptoms or signs typical for coeliac disease were classified as potential coeliac disease, including 29 cases in the first screening and 10 in the second screening (figure 1). In total, 12 353 children had negative serology in the screening.

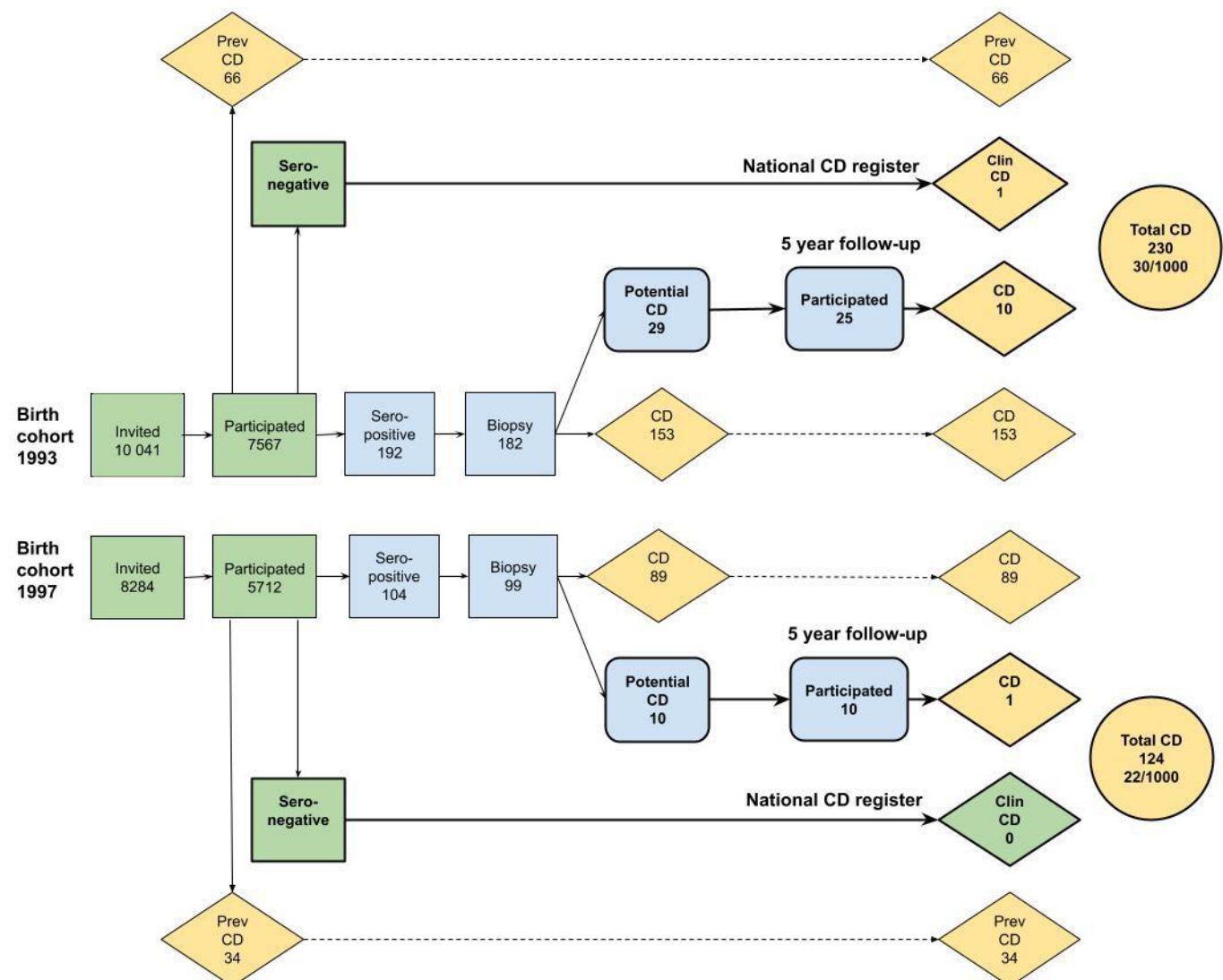


Figure 1 Screening for coeliac disease (CD) in two phases and 5-year follow-up of both children with positive serology (clinical appointment) and negative serology (register based) summarising total number of CD cases in two birth cohorts.

Five-year follow-up appointment

Five years after the screening, in 2011 and 2015, for the first and the second screening phases, respectively, we invited all children with positive serology for a clinical follow-up at the local paediatric clinic responsible for the ETICS study. Children with potential coeliac disease were recommended endoscopic small intestinal biopsy if serology remained positive. This clinical decision was based on the local analysis of anti-TG2-IgA.

Small intestinal biopsies obtained by endoscopy were evaluated by a local pathologist.

Follow-up using the National Swedish Childhood Coeliac Disease Register

To assess the risk for a clinical diagnosis of coeliac disease among the children with negative serology in the screening, we linked the group (n=12353) to the 'National Swedish Childhood Coeliac Disease Register'.¹⁵ The register is a nationwide prospective incidence register. All paediatric clinics performing small intestinal biopsies report new cases, mostly with full personal identity number allowing linkage on the individual level to other data sources.¹⁶ The register data have undergone quality assessment for the period 2010–2017 (unpublished data).

Statistical analyses

Data handling and statistical analyses were performed with Access 2016 (Microsoft, Redmond, Washington, USA). Descriptive statistics were used, and proportions were compared with the χ^2 test or Fisher's exact test. IBM SPSS V.26 2019 was used to compare means with two-way analysis of variance. Statistical significance was defined as $p < 0.05$.

RESULTS

Follow-up of children with positive serology

Of the 296 invited children, 230 (77%) came to the follow-up appointment at the paediatric clinic.

Twenty-four of 29 children with potential coeliac disease from the first screening phase, and all 10 potential cases from the second screening phase participated in the 5-year follow-up. Ten out of 24 from the first phase and 1 out of 10 from the second were diagnosed with coeliac disease rendering 11 new cases (figure 1), all confirmed with small intestinal biopsies regardless of level of anti-TG2-IgA. Details of the children with potential coeliac disease who had converted to disease are presented in table 1. Sex and level of anti-TG2-IgA at screening did not differ between the converting and non-converting group. EMA positivity was more common in the converting group (online supplemental table 1). More cases of potential coeliac disease were found in the first screening compared with the second (29 (0.38%) vs 10 (0.18%); $p=0.0012$). The proportion converting to coeliac disease was also higher, although not statistically significant (10 out of 29 (34%) vs 1 out of 10 (10%) $p=0.245$).

Follow-up of children with negative serology

Through linking the group of children with negative serology (n=12353) to the National Swedish Childhood Coeliac Disease Register, we identified one child from the first phase who was negative for anti-TG2-IgA at the screening but had been reported to the register with a coeliac disease diagnosis before the 5-year follow-up. This child had a diagnosis of type 1 diabetes and had been screened annually in line with prevailing guidelines. No new cases from the second phase were found (figure 1).

Table 1 Characteristics of children diagnosed with coeliac disease during the 5-year follow-up

ID	Sex	Anti-TG2-IgA at baseline (U/mL)	EMA-IgA titre at baseline	Local anti-TG2 IgA at follow-up/diagnosis (U/mL)	Standardised anti-TG2-IgA at follow-up (U/mL)	Symptoms	Histopathology and diagnostic considerations
Diagnosis before the 5-year follow-up							
1	F	2.8	1:5	Missing	0.5*	Abdominal pain	Marsh IIIa
2	F	5.6	1:10	26†	2.5*	Abdominal pain	Missing biopsy data, decrease in anti-TG2 IgA 5.6-26-14-2.5 on gluten-free diet
3	F	3.1	1:5	8.0†	0.5*	Gases, loose stools and fatigue	Marsh IIIb
4	M	6.9	1:5‡		0.8	Missing	Missing
5	F	2.7	1:20	5.0†	3.7*	Fatigue, abdominal pain and nausea	Marsh II
Diagnosis at follow-up							
6	M	12	1:20	40	Missing	Short stature	Marsh IIIa
7	F	6.6	1:10	25	Missing	Healthy	Marsh IIIa
8	F	4.0	1:5	95	22	Fatigue, upset stomach and constipation	Marsh I
9	F	6.2	1:5	14	3.8	Abdominal pain and upset stomach	Marsh IIIa
10	F	4.2	1:5	Missing	2.5	Abdominal pain	Marsh IIIb
11	F	3.9	1:5	Missing	22	Fatigue and upset stomach	Marsh 1

*At 5-year follow-up on a gluten-free diet.

†At diagnosis, before the 5-year follow-up.

‡EMA IgG and EMA IgA neg.

EMA, endomysial antibody.

DISCUSSION

In this study, we report that children with potential coeliac disease, that is, those who are seropositive but with normal small intestinal biopsies, are at high risk of conversion to coeliac disease during the following 5 years. However, in this age group, a negative screening test was associated with a very low risk for a clinical coeliac disease diagnosis during the same period.

The ETICS study was the first large population-based coeliac disease screening in children in Sweden.¹³ We showed that although active case finding is recommended, and screening of risk groups is implemented, most cases with coeliac disease remain undiagnosed.^{6, 7} In our opinion, a population-based screening is the only way to find most coeliac disease cases. Whether mass screening for coeliac disease should be introduced is a complex question under debate.^{11, 17, 18} We have previously shown that the performance of our screening strategy worked well with an estimated positive predictive value of 80% even though we used a reduced cut-off for anti-TG2-IgA.¹⁴ In 2012, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) introduced the possibility of a no-biopsy approach for diagnosing symptomatic children if anti-TG2-IgA is 10 times above the normal upper limit for the specific test. In our material, we showed that the same cut-off for a no-biopsy approach could also be used in a screening situation.¹⁹ In 2020, ESPGHAN revised their guidelines, and the no-biopsy now also applies to asymptomatic children. Applying these guidelines to the follow-up, one child could have been diagnosed without the biopsy. In a recently published health economic evaluation, we showed that coeliac disease screening of children aged 12 years can be considered cost effective, especially if the children diagnosed adhere to a gluten-free diet.²⁰ Of the children in the second phase of the screening, 69% reported to be always gluten free and 25% often gluten free at the 5-year follow-up.²¹ Corresponding numbers for the first phase were 56% and 29% for always gluten free and often gluten free, respectively (unpublished data).

One additional important question concerns the natural history of coeliac disease. In this study, we had the possibility to follow 39 cases of potential coeliac disease for 5 years and found that about one-third developed coeliac disease within this period. However, it is notable that there was a considerable difference between the two birth cohorts. The first screening phase included the birth cohort of 1993, born during a coeliac disease epidemic and they had significantly higher prevalence also at the follow-up compared with the second phase of the study when the 1997 birth cohort was screened.⁶ We cannot exclude that the environmental factors increasing the risk for coeliac disease in the 1993 cohort also affected the risk for potential coeliac disease and conversion to coeliac disease. In line with the findings from our 1997 cohort, Volta *et al*²² followed 16 asymptomatic adults with potential coeliac disease over 3 years and only one converted. Auricchio *et al* followed cases over a longer period (12 years) and found that 43% of 280 potential cases developed coeliac disease.²³ A limitation of our study was that the number of potential coeliac disease cases was relatively low, and not everyone participated in the follow-up, making our prevalence estimates somewhat underestimated. We relied on local routine diagnostic assessments, but serological findings were verified with a second analysis for the respective cohort. We conclude that children who have tested positive to anti-TG2-IgA at one time point need to be followed for a long period because of high risk of developing coeliac disease later in life.

Because coeliac disease can present at any time during the life span, another important question is whether a mass screening must be repeated and, in that case, how often. When we followed up the seronegative children through linkage between the coeliac disease mass screening study and the National Swedish Childhood Coeliac Disease Register, we could only identify one new case of coeliac disease 5 years later. This child belonged to a well-known risk group who are screened annually for coeliac disease. In the latter cohort, we did not find any new cases. This indicates that if testing negative for anti-TG2-IgA the risk of being diagnosed with coeliac disease through routine clinical practice within 5 years after a mass screening is very low in this age group. However, there are some limitations to this conclusion. We know that most coeliac disease cases are reported to the National Swedish Childhood Coeliac Disease Register but not all. Thus, we cannot exclude that we missed some children. Only diagnosed cases are reported to the register, meaning that those who were overlooked in clinical care and who were never tested again because they had negative serology in the study or were truly asymptomatic would be missed. This could contribute to an underestimation of new coeliac disease cases. To gain definitive information about this group would require a second screening.

CONCLUSION

Potential coeliac disease requires follow-up because of the high risk of conversion to disease with enteropathy. The risk of receiving a clinical diagnosis within 5 years from a screening is very low indicating that a possible repeated screening can wait longer than this.

Acknowledgements We would like to thank Carina Lagerqvist for her work with the study biobank, Susanne Walther for the administration of the National Swedish Childhood Coeliac Disease Register, all collaborators within the ETICS study and of course all participating children and families.

Contributors AI, AC, AM, FN, LS and OS were responsible for the conceptualisation of the study. FN performed the statistical analyses. OS, FN and AM wrote the manuscript. OS, LH, MvdP, LS and CW were responsible for data collection. All authors contributed to interpretation of study findings and revision of the manuscript and have approved the submitted version of the manuscript. OS accepts full responsibility for the finished work, had access to the data, and controlled the decision to publish.

Funding Open access funding was provided by Umeå University. This original study was funded by the European Union-supported project FP6-2005-FOOD-4B-36383-PREVENTCD, the Swedish Research Council (grants 521-2004-7093 and 521-2007-2953), the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning (grants 222-2004-1918 and 222-2007-1394) and the Swedish Council for Working Life and Social Research (grant 2005-0802). We also received funding from Västerbotten County Council for this specific follow-up (grant RV-238151).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethical Review Board of Umeå University, Umeå, Sweden (2004-156 and 2020-6257). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data included in this study are available after request and discussion with the corresponding author.

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