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ORIGINAL ARTICLE

# Regional Swedish study found that one in seven coeliac patients experienced loss of follow up during childhood

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## Abstract

**Aim:** To examine the clinical follow up of paediatric coeliac disease and the rate of loss of follow up during childhood, for which data are scarce.

**Methods:** In a cohort of coeliac children diagnosed in 2013–2018 in Gothenburg, Sweden, we retrospectively explored the follow-up practice of paediatric coeliac disease until June 2021. We used medical records from hospital-based paediatric gastroenterology and general paediatric outpatient clinics, laboratory records, and questionnaires. Loss of follow up was defined no coeliac disease-related follow up or tissue transglutaminase test over the past 2 years of study enrolment.

**Results:** We included 162 children (58% girls) aged 7.8–18.2 years (average 12.7). Most participants (76%) were followed at general paediatric outpatient clinics rather than hospital-based clinics. After 2.3–8.8 (average 5.3) years since diagnosis, 23 patients (14%; 95% confidence interval, 9%–21%) had been lost to follow up. Patients with loss of follow up were more often boys (61% versus 39%, $p = 0.08$), with a somewhat longer average disease duration of 5.8 versus 5.2 years ($p = 0.11$). There were no between-group differences in socio-economic characteristics and patient-reported experience measures of coeliac disease care.

**Conclusion:** One in seven coeliac patients may experience loss of follow up during childhood.

KEYWORDS
celiac disease, coeliac disease, loss of follow up, tissue transglutaminase

## 1 | INTRODUCTION

Coeliac disease is one of the most common conditions in childhood, affecting 1% of children worldwide.[1] The disease is triggered by gluten from wheat and related cereals causing small-intestinal villous atrophy.[2] Children with untreated coeliac disease may suffer from anaemia, failure to thrive, and impaired bone health.[3] While a strict gluten-free diet may alleviate symptoms and heal the intestinal

**Abbreviations:** SD, standard deviation.

mucosa, maintaining such a diet can be problematic in the long run.[4] follow up of paediatric coeliac disease aims to ensure a strict gluten-free diet, monitor symptoms, and prevent disease-associated complications.[5–7]

Despite the high prevalence and excess morbidity risk in coeliac disease, data on its follow-up care in childhood are scarce, including the methods used to monitor dietary adherence, disease remission, and complications.[6,7] Related to this knowledge gap, there have until recently been no evidence-based paediatric guidelines on coeliac disease follow up, and practices have varied widely across clinics.[8] Only two studies have examined the proportion of coeliac patients with loss of follow up in childhood, with estimates ranging from 35% to 57%.[9,10] However, these estimates considered loss of follow up from hospital-based outpatient care by paediatric gastroenterologists, rather than *any* coeliac disease care,[9,10] or included potential coeliac disease,[9] a possible preclinical manifestation of coeliac disease where the need for long-term follow up is unknown.[11] There are few data on predictors for loss of follow up of coeliac disease in childhood.[10]

Using data from a Swedish regional cohort of paediatric coeliac patients, we aimed to describe the practice and frequency of follow up of children with coeliac disease, as well as the proportion of patients lost to follow up. We also sought to examine potential predictors for loss of follow up, such as socio-economic characteristics and patient experience of coeliac disease care.

**Key notes**

- Little is known about the clinical follow up of paediatric coeliac disease and the rate of loss of follow up during childhood.
- In this regional cohort of 162 Swedish children with coeliac disease, one in seven patients (14%) experienced loss of follow up during childhood
- Loss of follow up was not significantly linked to socio-economic characteristics or patient-reported experience measures of coeliac disease care.

## 2 | METHODS

This cohort study included 162 school-aged children with coeliac disease. We explored the follow-up practice for paediatric coeliac disease and the rate of loss of follow up in children through a combination of retrospectively collected data from patient records and study-specific questionnaires.

### 2.1 | Study setting and sample

This study was based on a cohort of paediatric patients diagnosed with coeliac disease between 2013 and 2018 at Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden.[12] In 2013–2018, local guidelines required all paediatric coeliac disease, including non-biopsy verified coeliac disease to be diagnosed at the paediatric gastroenterology section at Queen Silvia Children's Hospital. Since 2015, local guidelines recommend all follow up of coeliac disease be conducted at general paediatric outpatient clinics. Exceptions include children with co-occurring type 1 diabetes cared for by paediatric endocrinologists. Before 2015, paediatric coeliac patients were followed at the gastroenterology section at Queen Silvia Children's Hospital until tissue transglutaminase normalisation and then transferred to general paediatric outpatient clinics.

We used hospital diagnostic records to identify all 484 patients aged 8-<18 years on December 31, 2020, with at least one International Classification of Disease-10 code K90.0 for coeliac disease between 2013 and 2018. The study was confined to coeliac disease diagnosed in 2013–2018 to ensure homogenous diagnostic criteria and a minimum of 2 years of follow up from diagnosis until study enrolment in January–June 2021.[13] After patient chart review, 336 patients were considered to fulfil national diagnostic guidelines for coeliac disease. Among these 336 coeliac patients, stratified by calendar year of diagnosis (2013–2018), we randomly selected 243 children who were invited for study participation, out of whom 162 agreed to participate, yielding a participation rate of 67% (Figure 1). We sought to invite children aged 8–18 years to match the ages for which the study questionnaires had been validated; however, four children, who fell narrowly outside that age cut-off, were also included (age range 7.8–18.2 years).

According to the Swedish adaptation of the 2012 guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition,[13] coeliac disease diagnoses required confirmation of small-intestinal intraepithelial lymphocytosis with crypt hyperplasia or villous atrophy, Marsh score 2–3.[14] A non-biopsy diagnosis of coeliac disease required related symptoms, permissive human leucocyte antigen haplotypes, and repeated IgA tissue transglutaminase 10 times the upper limit of normal (≥70 U/ml). Because of the unavailability of endomysial antibody tests in Sweden, national guidelines do not require such a test for a non-biopsy coeliac disease diagnosis.[5]

### 2.2 | Patient chart data

#### 2.2.1 | Coeliac disease diagnosis and follow up

The time of coeliac disease diagnosis was defined as the date of diagnostic biopsy or, in non-biopsy verified diagnoses, the date when patients were informed of their diagnosis. We retrieved patient chart data on small-intestinal biopsy results. We also retrieved results from the following laboratory tests performed

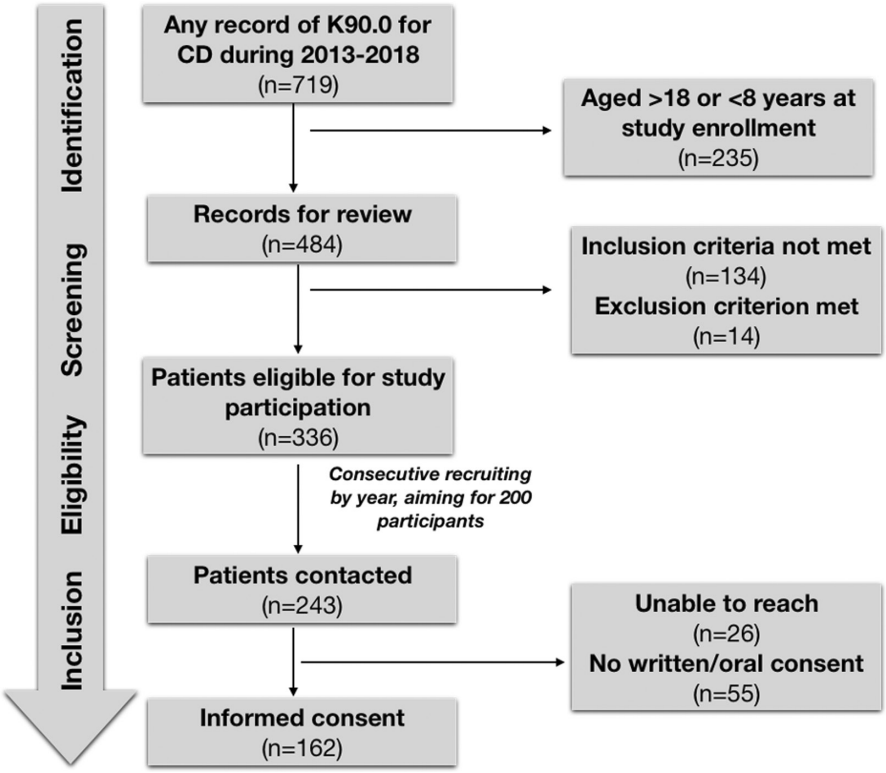


**FIGURE 1** Flowchart of the formation of the study sample. We identified all 719 patients at our hospital with the international classification of diseases-code K90.0 for coeliac disease (CD) in 2013–2018. Non-included patients ($n = 134$) were non-coeliac disease-patients ($n = 36$), lacked human leukocyte antigen data ($n = 50$), or otherwise did not fulfil diagnostic criteria for coeliac disease ($n = 48$). Patients excluded had immigrated ($n = 11$), emigrated ($n = 2$), or protected identity ($n = 1$). Recruitment stopped at >200 interested, leaving 93 eligible patients. Fifty-five patients declined participation or did not provide written informed consent. We retrieved medical/laboratory data for all participants and questionnaire data for 146 participants. One patient was 7.8 years and three were 18.0–18.2 years old at enrolment.

from 3 months before until 1 month after coeliac diagnosis: tissue transglutaminase, human leucocyte antigen, haemoglobin, thyroid function tests, iron storage tests, liver function tests, 25-hydroxyvitamin D, folate, and cobalamin. We recorded all follow-up visits for coeliac disease at Queen Silvia Children's Hospital and results from any control biopsies and bone mineral density measurements. We also reviewed all follow-up visits from January 1, 2019, until June 30, 2021, at all $n = 7$ general paediatric outpatient clinics in the Gothenburg metropolitan area. Patient chart data were retrieved and assessed by the first author (MU) in mid-2021. Data inconsistencies were resolved in discussion with a second reviewer (KM).

#### 2.2.2 | Loss of follow up

We defined loss of follow up as no documented counselling for coeliac disease by a physician or dietician or measurement of tissue transglutaminase over the past 2 years (<24 months) at study enrolment (January–June 2021). This 2-year time lag was motivated by national and international guidelines recommending at least annual to biannual follow up for children with coeliac disease.[5,15]

### 2.3 | Questionnaire data

All questionnaires were administered through an electronic case report form (Medicase AB). Questionnaires were completed by a parent or jointly with the child.

#### 2.3.1 | Background characteristics

We retrieved data on patient characteristics that may influence the continuation of follow up: parental country of birth, education level, employment status, patients' current and past medical history, and family history of chronic immune-mediated disease (Table 1).

#### 2.3.2 | Questionnaire data on coeliac-related symptoms and care

We retrieved parent-reported and self-reported data on disease-related symptoms at the time of diagnosis (Table 2). In addition to patient chart data on follow up, we surveyed the patients' perspectives on how the follow up was routinely conducted. This survey included methods used to evaluate dietary adherence, nutritional status, symptoms, health-related quality of life, and use of laboratory tests. We also surveyed their recommended use of nutritional supplements.

#### 2.3.3 | Patient-reported experience measure

We surveyed patient-reported experience measures of coeliac disease care using the generic National Paediatric Outpatient Survey.[16] Children aged 15–18 years were asked to answer the questionnaire themselves and younger patients with the help of a parent. The questionnaire consisted of 31 items capturing seven aspects of care: overall

**TABLE 1** Sociodemographic characteristics and medical history for coeliac disease patients with loss of follow up vs. continued follow up.

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) | *p*-Value |
|---|---|---|---|---|
| Age (years) | | | | |
| Mean (SD) | 12.7 (2.8) | 12.7 (2.6) | 13.2 (3.6) | 0.68 |
| Min; Max | 7.8; 18.2 | 8.0; 18.2 | 7.8; 18.2 | |
| Sex | | | | |
| Girls | 94 (58%) | 85 (61%) | 9 (39%) | 0.08 |
| Age of parent (years) | | | | |
| Mean (SD) | 44.5 (5.1) | 44.2 (5.1) | 46.1 (4.9) | 0.29 |
| Min; Max | 31; 55 | 31; 55 | 37; 54 | |
| Years since coeliac disease diagnosis | | | | |
| Mean (SD) | 5.3 (1.7) | 5.2 (1.8) | 5.8 (1.6) | 0.11 |
| Min; Max | 2.3; 8.8 | 2.3; 8.8 | 3.1; 8.1 | |
| Parental education level | | | | |
| Secondary school | 37/152 (24%) | 31/131 (24%) | 6/21 (29%) | 0.77 |
| University/college 0–3 years | 42/152 (28%) | 39/131 (30%) | 3/21 (14%) | |
| University/college >4 years | 73/152 (48%) | 61/131 (47%) | 12/21 (57%) | |
| Parental employment | | | | |
| Employed | 142/152 (93%) | 122/131 (93%) | 20/21 (95%) | 0.78 |
| Sick leave/unemployed | 3/152 (2%) | 3/131 (2%) | 0/21 (0%) | |
| Student/parental leave | 7/152 (5%) | 6/131 (5%) | 1/21 (5%) | |
| Parental cohabitation | | | | |
| No | 25/152 (16%) | 22/131 (17%) | 3/21 (14%) | 1.00 |
| Yes | 127/152 (84%) | 109/131 (83%) | 18/21 (86%) | |
| Parental country of birth | | | | |
| Sweden/Sweden | 124/150 (83%) | 105/129 (81%) | 19/21 (91%) | 0.49 |
| Sweden/other | 20/150 (13%) | 19/129 (15%) | 1/21 (5%) | |
| Other/other | 6/150 (4%) | 5/129 (4%) | 1/21 (5%) | |
| Year of diagnosis | | | | |
| 2013[a] | 25/162 (15%) | 21/139 (15%) | 4/23 (17%) | 0.13 |
| 2014 | 30/162 (19%) | 22/139 (16%) | 8/23 (35%) | |
| 2015 | 27/162 (17%) | 24/139 (17%) | 3/23 (13%) | |
| 2016 | 24/162 (15%) | 21/139 (15%) | 3/23 (13%) | |
| 2017 | 30/162 (19%) | 28/139 (20%) | 2/23 (9%) | |
| 2018 | 26/162 (16%) | 23/130 (17%) | 3/23 (13%) | |
| Medical history | | | | |
| Gastrointestinal complaints | 94/135 (70%) | 83/118 (70%) | 11/17 (65%) | 0.34 |
| Poor weight gain/short stature | 20/135 (15%) | 15/118 (13%) | 5/17 (30%) | |
| Asthma/allergy | 9/135 (7%) | 9/118 (8%) | 0/17 (0%) | |
| Eczema | 2/135 (2%) | 2/118 (2%) | 0/17 (0%) | |
| Other[b] | 10/135 (7%) | 9/118 (8%) | 1/17 (6%) | |
| Any physician's visit over the past 12 months | | | | |
| No | 83/162 (51%) | 66/139 (48%) | 17/23 (74%) | 0.03 |
| Yes | 79/162 (49%) | 73/139 (53%) | 6/23 (26%) | |
| Any hospitalisation before study enrollment | | | | |
| No | 107/150 (71%) | 91/129 (71%) | 16/21 (76%) | 0.81 |
| Yes | 43/150 (29%) | 38/129 (30%) | 5/21 (24%) | |

TABLE 1 (Continued)

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) | *p*-Value |
|---|---|---|---|---|
| Currently patient[c] at Qeen Silvia Children's Hospital | | | | |
| No | 135/150 (90%) | 114/129 (88%) | 21/21 (100%) | 0.18 |
| Yes | 15/150 (10%) | 15/129 (12%) | 0/21 (0%) | |
| Family history of… | | | | |
| Coeliac disease | 37/138 (27%) | 31/120 (26%) | 6/18 (33%) | 0.68 |
| Autoimmune liver disease | 2/162 (1%) | 1/139 (1%) | 1/23 (4%) | 0.53 |
| Psoriasis | 13/162 (8%) | 9/139 (7%) | 4/23 (17%) | 0.18 |
| Rheumatic disease | 9/150 (6%) | 9/129 (7%) | 0/23 (0%) | 0.49 |
| Thyroid disease | 25/162 (15%) | 23/135 (17%) | 2/23 (9%) | 0.54 |
| Type 1 diabetes | 10/162 (6%) | 8/133 (6%) | 2/23 (9%) | 0.86 |
| Patient association for coeliac disease | | | | |
| Yes, member | 73/146 (50%) | 65/125 (52%) | 8/21 (38%) | 0.35 |

*Note*: Loss of follow up was defined as no registered visit for coeliac disease and no registered tissue transglutaminase over the past 2 years.
Abbreviation: SD = Standard deviation.

[a] One patient received a preliminary coeliac disease diagnosis in December 2012, which was confirmed in January 2013.

[b] Other diseases included renal or urinary tract disease, anaemia, epileptic seizures, headache, neuropsychiatric disorders, overweight/obesity, congenital syndrome, psychiatric disorders, rheumatic disease, thyroid disease, type 1 diabetes, and developmental delay.

[c] Visits over the past 6 months to Queen Silvia Children's Hospital (QSCH).

impression, emotional support, patient involvement, respect and responsiveness, continuity and coordination, information, and accessibility. Each item was graded on a 5-point Likert scale, with scores of 4–5 indicating a positive care experience. We calculated each participant's average dimension score as the total score divided by the number of responded items for that dimension. Reported care experience represents the percentage of responders with an average dimension score of ≥4, indicating a positive care experience for that dimension.

## 2.4 | Statistical analyses

We compared background characteristics, coeliac disease follow-up practice, and patient-reported experience measures for coeliac disease care in children with loss of follow up and continued follow up. Reported estimates were based on nonmissing values if not stated otherwise. Missingness, as reported in Tables 1–3, was chiefly related to incomplete answered questionnaires. For between-group comparisons, we used Fisher's Exact test for dichotomous variables and the Mantel–Haenszel chi-square test for ordered categorical variables. The chi-square test was used for nonordered categorical variables and the Mann–Whitney U test for continuous variables.

### 2.4.1 | Sensitivity analysis: assessment of potential self-selection bias

To examine the potential impact of selection bias on our results, we compared age, sex, and calendar year of coeliac disease diagnosis between study participants (*n* = 162) and eligible coeliac patients not included in the study (*n* = 81) (Figure 1, Table S1).

Data were analysed using SAS, version 9.4 (SAS Institute, Inc.).

## 2.5 | Ethics

The study has been approved by the Swedish Ethical Review Authority (No. 2020-06033). Parental informed consent was obtained from children 8–14 years, with assent from children aged 12–14 years. Children ≥15 years provided their informed consent. Data were pseudonymised before analyses.

# 3 | RESULTS

The mean age at study enrolment was 12.7 years (SD 2.7 years, range 7.8–18.2 years). The average duration since coeliac disease diagnosis was 5.3 years (SD 1.7 years, range 2.3–8.8 years). Most of the participants, 98 out of 162 (58%), were girls and slightly over a quarter, 37 out of 138 (27%), had a family history of coeliac disease (Table 1).

A majority of the children, 94 out of 162 (70%), had a history of gastrointestinal complaints and 15 out of 150, reported follow up at Queen Silvia Children's Hospital for a condition other than coeliac disease. Some 10% of the patients had been identified through serological screening as part of follow up for type 1 diabetes or other high-risk conditions (Table 2). In total, 97 out of 162 (60%) participants had been diagnosed using a non-biopsy approach.

## 3.1 | Clinical follow-up practice

Coeliac disease follow up was usually conducted at general paediatric outpatient clinics, and only rarely by primary care physicians (Table 3). While psychologists and nurses seldom conducted follow-up care, 92 out of 148 participants (62%) had experienced dietician-led follow-up visits for coeliac disease (Table 3; Table S2). Symptoms,

**TABLE 2** Diagnostic characteristics of coeliac disease in children with loss of follow up and continued follow up.

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) | *p* Value |
|---|---|---|---|---|
| Age at diagnosis (years) | | | | |
| Mean (SD) | 7.5 (3.2) | 7.5 (3.1) | 7.4 (3.9) | 0.95 |
| Median; (Min-Max) | 7.3; (0.8–15.0) | 7.3; (0.8–15.0) | 7.3 (0.91–14.6) | |
| Self/parent-reported symptom duration at diagnosis (years) | | | | |
| Mean (SD) | 1.2 (1.8) | 1.3 (1.9) | 0.7 (0.6) | 0.51 |
| Human Leukocyte Antigen haplotype | | | | |
| DQ2.5/2.5 | 37/162 (23%) | 34/139 (25%) | 3/23 (13%) | 0.59 |
| DQ2.2/2.2 | 2/162 (1%) | 2/139 (1%) | 0/23 (0%) | |
| DQ8/8 | 7/162 (4%) | 6/139 (4%) | 1/23 (4%) | |
| DQ2.5/2.2 | 20/162 (12%) | 15/139 (11%) | 5/23 (22%) | |
| DQ2.5/2.2/8/X[a] | 96/162 (59%) | 82/139 (59%) | 14/23 (61%) | |
| Diagnostic small-intestinal biopsy[22] | | | | |
| Performed | 65/162 (40%) | 60/139 (43%) | 5/23 (22%) | 0.08 |
| Marsh 2 | 3/65 (5%) | 3/60 (5%) | 0/5 (0%) | |
| Marsh 3 | 62/65 (95%) | 57/60 (95%) | 5/5 (100%) | 0.63 |
| Coeliac disease investigation initiated due to… | | | | |
| Symptoms[b] | 110/145 (76%) | 93/125 (74%) | 17/20 (85%) | 0.77 |
| Symptoms and heredity[c] | 15/145 (10%) | 13/125 (10%) | 2/20 (10%) | |
| Symptoms and type 1 diabetes[5] | 1/145 (1%) | 1/125 (1%) | 0/20 (0%) | |
| Symptoms and abnormal laboratory test | 6/145 (4%) | 5/125 (4%) | 1/20 (5%) | |
| Heredity of coeliac disease[c] | 9/145 (6%) | 9/125 (7%) | 0/20 (0%) | |
| Type 1 diabetes[d] | 4/145 (3%) | 4/125 (3%) | 0/20 (0%) | |

*Note*: No comparison between children with loss of follow up vs. continuous follow up was statistically significant (all *p*-values ≥0.08).

Abbreviation: SD = Standard deviation.

[a] X meaning another human leukocyte antigen haplotype than DQ2.5, DQ2.2, or DQ8.

[b] Symptoms of coeliac disease, e.g., abdominal pain, constipation.

[c] First-degree relatives with coeliac disease.

[d] Coeliac disease screening due to type 1 diabetes.

dietary adherence, and health-related quality of life were routinely addressed during follow up. Such assessments were mostly performed through unstructured interviews with the patient rather than using specific questionnaires (Table 3).

### 3.1.1 | Assessment of disease remission and complications

Figure 2 illustrates the timing of tissue transglutaminase measurements and the average tissue transglutaminase trajectory during coeliac disease follow up. After 12 months since diagnosis, tissue transglutaminase had normalised in 60% of the children (95% confidence interval [CI], 49%–70%), and after 36 months in 86% (95% CI, 77%–92%) (Figure 3). Next to tissue transglutaminase, haemoglobin was the second most common laboratory test performed. Iron storage, thyroid function, liver enzymes, 25-hydroxyvitamin D, cobalamin, and folate were not routinely measured during follow up (Table S3). A follow-up biopsy on a gluten-free diet had been performed in eleven children. Out of these, eight children had Marsh 0–1 indicating normal mucosa, two patients had Marsh 2 and one patient Marsh 3 (Table 3). Bone density measurement was performed on one patient.

## 3.2 | Loss of follow up

At study enrolment, 23 of 162 patients (14%, 95% CI 9%–21%) had experienced loss of follow up, meaning no coeliac disease-related consultation or tissue transglutaminase measurement over the past

**TABLE 3** Coeliac disease follow-up practice of children according to medical records and self−/parent-reported data grouped by frequency categories.[a]

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) |
|---|---|---|---|
| Self−/parent-reported data | | | |
| No. of coeliac disease-related follow-up visits | | | |
| Mean (SD) | 5.9 (3.8) | 6.0 (3.8) | 2.8 (0.8) |
| (Min; max) | (1; 20) *n* = 115 | (1; 2) *n* = 110 | (2; 4) *n* = 5 |
| Category of healthcare professional/clinic for coeliac disease follow up | | | |
| Paediatrician, hospital-based paediatric outpatient clinic | | | |
| Never/rarely | 91/123 (74%) | 86/117 (74%) | 5/6 (83%) |
| Sometimes | 7/123 (6%) | 7/117 (6%) | 0/6 (0%) |
| Often | 4/123 (3%) | 4/117 (3%) | 0/6 (0%) |
| Always/almost always | 21/123 (17%) | 20/117 (17%) | 1/6 (17%) |
| Paediatrician, general paediatric outpatient clinic | | | |
| Never/rarely | 37/123 (31%) | 35/117 (30%) | 2/6 (33%) |
| Sometimes | 8/123 (7%) | 8/117 (7%) | 0/6 (0%) |
| Often | 10/123 (8%) | 10/117 (9%) | 0/6 (0%) |
| Always/almost always | 68/123 (55%) | 64/117 (55%) | 4/6 (67%) |
| Physician, primary care | | | |
| Never/rarely | 100/118 (85%) | 94/112 (84%) | 6/6 (100%) |
| Sometimes | 7/118 (6%) | 7/112 (6%) | 0/6 (0%) |
| Often | 4/118 (3%) | 4/112 (4%) | 0/6 (0%) |
| Always/almost always | 7/118 (6%) | 7/112 (6%) | 0/6 (0%) |
| Nurse | | | |
| Never/rarely | 83/117 (71%) | 78/111 (70%) | 5/6 (83%) |
| Sometimes | 18/117 (15%) | 18/111 (16%) | 0/6 (0%) |
| Often | 5/117 (4%) | 5/111 (5%) | 0/6 (0%) |
| Always/almost always | 11/117 (9%) | 10/111 (9%) | 1/6 (17%) |
| Psychologist | | | |
| Never/rarely | 112/117 (96%) | 106/111 (95%) | 6/6 (100%) |
| Sometimes | 3/117 (2.6%) | 3/111 (2%) | 0/6 (0%) |
| Often | 1/117 (1%) | 1/111 (1%) | 0/6 (0%) |
| Always/almost always | 1/117 (1%) | 1/111 (1%) | 0/6 (0%) |
| Dietician | | | |
| Never/rarely | 79/122 (65%) | 74/117 (63%) | 5/5 (100%) |
| Sometimes | 27/122 (22%) | 27/117 (23%) | 0/5 (0%) |
| Often | 10/122 (8%) | 10/117 (9%) | 0/5 (0%) |
| Always/almost always | 6/122 (5%) | 6/117 (5%) | 0/5 (0%) |
| Physicians' follow up: estimate how often the following are part of coeliac disease follow up… | | | |
| Evaluation of symptoms… | | | |
| a. …by interview | | | |
| Never/rarely | 11/126 (9%) | 11/120 (92%) | 0/6 (0%) |
| Sometimes | 10/126 (8%) | 10/120 (8%) | 0/6 (0%) |
| Often | 13/126 (10%) | 13/120 (11%) | 0/6 (0%) |
| Always/almost always | 92/126 (73%) | 86/120 (72%) | 6/6 (100%) |
| b. …trough questionnaire | | | |
| Never/rarely | 118/124 (95%) | 11/118 (96%) | 5/6 (83%) |
| Sometimes | 3/124 (2%) | 3/118 (3%) | 0/6 (0%) |

(Continues)

TABLE 3 (Continued)

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) |
|---|---|---|---|
| Often | 1/124 (1%) | 1/118 (1%) | 0/6 (0%) |
| Always/almost always | 2/124 (2%) | 1/118 (1%) | 1/6 (17%) |
| Evaluation of Health-related quality of life… | | | |
| a. …by interview | | | |
| Never/rarely | 41/126 (33%) | 40/120 (33%) | 1/6 (17%) |
| Sometimes | 25/126 (20%) | 24/120 (20%) | 1/6 (17%) |
| Often | 15/126 (12%) | 15/120 (13%) | 0/6 (0%) |
| Always/almost always | 45/126 (36%) | 41/120 (34%) | 4/6 (67%) |
| b. …trough questionnaire | | | |
| Never/rarely | 120/123 (97%) | 115/117 (98%) | 5/6 (83%) |
| Sometimes | 2/123 (2%) | 2/117 (2%) | 0/6 (0%) |
| Often | 0/123 (0%) | 0/117 (0%) | 0/6 (0%) |
| Always/almost always | 1/123 (1%) | 0/117 (0%) | 1/6 (17%) |
| Evaluation of dietary adherence… | | | |
| a. …by interview | | | |
| Never/rarely | 23/126 (18%) | 23/120 (19%) | 0/6 (0%) |
| Sometimes | 19/126 (15%) | 17/120 (14%) | 2/6 (33%) |
| Often | 14/126 (11%) | 13/120 (11%) | 1/6 (17%) |
| Always/almost always | 70/126 (56%) | 67/120 (56%) | 3/6 (50%) |
| b. …trough questionnaire | | | |
| Never/rarely | 112/124 (90%) | 116/118 (98%) | 6/6 (100%) |
| Sometimes | 1/124 (1%) | 1/118 (1%) | 0/6 (0%) |
| Often | 1/124 (1%) | 1/118 (1%) | 0/6 (0%) |
| Always/almost always | 0/124 (1%) | 0/118 (1%) | 0/6 (0%) |
| Weight and height measurement | | | |
| Never/rarely | 5/126 (4%) | 5 (120 (5%) | 0/6 (0%) |
| Sometimes | 11/126 (9%) | 11/120 (9%) | 0/6 (0%) |
| Often | 10/126 (8%) | 10/120 (8%) | 0/6 (0%) |
| Always/almost always | 100/126 (79%) | 94/120 (78%) | 6/6 (100%) |
| Physical examination | | | |
| Never/rarely | 26/125 (21%) | 24/119 (20%) | 2/6 (33%) |
| Sometimes | 16/125 (13%) | 15/119 (13%) | 1/6 (17%) |
| Often | 20/125 (16%) | 19/119 (16%) | 1/6 (17%) |
| Always/almost always | 63/125 (50%) | 61/119 (51%) | 2/6 (33%) |
| Data from patients' medical records | | | |
| follow-up biopsy | | | |
| No | 151/162 (93%) | 128/139 (92%) | 23/23 (100%) |
| Yes | 11/162 (7%) | 11/139 (8%) | 0/23 (0%) |
| Marsh 0 | 7/11 (64%) | 7/11 (64%) | |
| Marsh 1 | 1/11 (9%) | 1/11 (9%) | |
| Marsh 2 | 2/11 (18%) | 2/11 (18%) | |
| Marsh 3 | 1/11 (9%) | 1/11 (9%) | |
| *Any hospital-based* coeliac disease follow-up visit | 92/162 (57%) | 74/139 (53%) | 18/23 (78%) |
| Non-responsive coeliac disease | 5/92 (5%) | 5/74 (7%) | 0/18 (0%) |
| Non-adherent to gluten-free diet | 7/92 (8%) | 5/74 (7%) | 2/18 (11%) |

TABLE 3 (Continued)

| Variable *n* (%) | Total (*n* = 162) | Continued follow up (*n* = 139) | Loss of follow up (*n* = 23) |
|---|---|---|---|
| Diabetes/endocrine | 19/92 (21%) | 17/74 (23%) | 2/18 (11%) |
| Investigation for other diseases | 4/92 (4%) | 4/74 (5%) | 0/18 (0%) |
| Irritable bowel syndrome | 1/92 (1%) | 1/74 (1%) | 0/18 (0%) |
| Inflammatory bowel disease | 1/92 (1%) | 1/74 (1%) | 0/18 (0%) |
| Other[b] | 55/92 (60%) | 41/74 (55%) | 14/18 (78%) |

*Note*: Loss of follow up was defined as no visit for coeliac disease and no recorded tissue transglutaminase over the past 2 years.

Abbreviation: SD = Standard deviation.

[a] Verbal frequency expressions (i.e., "often," "always," etc.) were selected to be equidistantly distributed and discriminatory (i.e., while the interpretation of some terms may overlap among responders, "often" usually have a different meaning than "always").

[b] Until 2015, local guidelines recommended continued follow up at a paediatric gastroenterology outpatient clinic until coeliac diagnosis has been confirmed through tissue transglutaminase serology normalisation, symptom resolution, and/or mucosal healing on control biopsy.

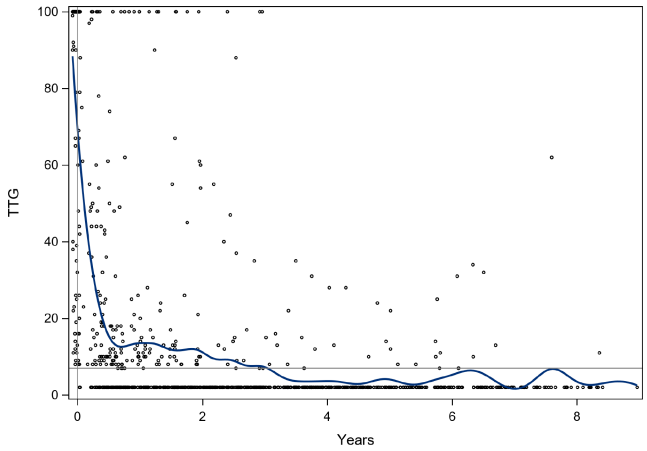


FIGURE 2 Individual and average tissue transglutaminase (TTG) measurements (U/ml) since diagnosis of coeliac disease (year "0"). Each tissue transglutaminase measurement is displayed as a circle with the blue line representing the average tissue transglutaminase over time plotted using a penalised B-spine. The thin vertical line denotes the cut-off for positive tissue transglutaminase (7 U/ml).

24 months. Of these 23 patients, 13 had a coeliac disease follow-up visit or tissue transglutaminase measurement during the past 36 months. Notably, one third of the children with *continued* follow up for coeliac disease, 44 out of 127 (35%), reported no regular dietetic consultation.

Figure 4 depicts the timing of the last coeliac disease-related follow-up visit and tissue transglutaminase measurement in children with loss of follow up and continued follow up. Patients with loss of follow up were more often boys (61%), compared to those with continued follow up (39%, $p = 0.08$). Those with loss of follow up also had a somewhat longer average duration since diagnosis compared to children with continued follow up (5.8 vs. 5.2 years; $p = 0.11$) (Table 2). However, socio-economic characteristics, including parental education level and country of birth, were similar between these groups of patients (Table 1).

Out of the 23 patients with loss of follow up, 16 stated a reason for no follow up; 10 participants had not received an invitation for an appointment, three participants saw no need for long-term follow up, and three reported "do not know" to why they had not had follow for coeliac disease.

### 3.3 | Patient-reported experience measures

Using the National Paediatric Outpatient Survey, we found a score of 87 (SD 18) for the "overall impression" of coeliac disease care; the score ranges from 0 to 100 with higher scores indicating a better care experience. The reported care experience was similar both overall and across sub-dimensions of patient-reported experience measures, for children with loss of follow up and continued follow up for coeliac disease (all *p*-values ≥0.09) (Table S4).

### 3.4 | Assessment of potential self-selection bias

To investigate potential selection bias related to non-participation we compared selected study characteristics between study participants ($n = 162$) and non-eligible coeliac patients not included in the study ($n = 81$). While non-participants were on average somewhat older than the study participants, 13.6 versus 12.7 years old ($p$ value = 0.03), there were no significant differences in sex and year of coeliac disease diagnosis (Table S1).

## 4 | DISCUSSION

In this regional cohort study, we explored the follow-up practice of coeliac disease in general and hospital-based paediatric outpatient care settings. After an average of 5 years since diagnosis, one in seven coeliac patients had a loss of follow up. Almost one-third of the patients with continued follow up lacked regular dietetic consultations. Patients with loss of follow up were more often boys and had a slightly longer average disease duration compared to those with continued follow up of coeliac disease, but without significant differences in socio-economic characteristics.

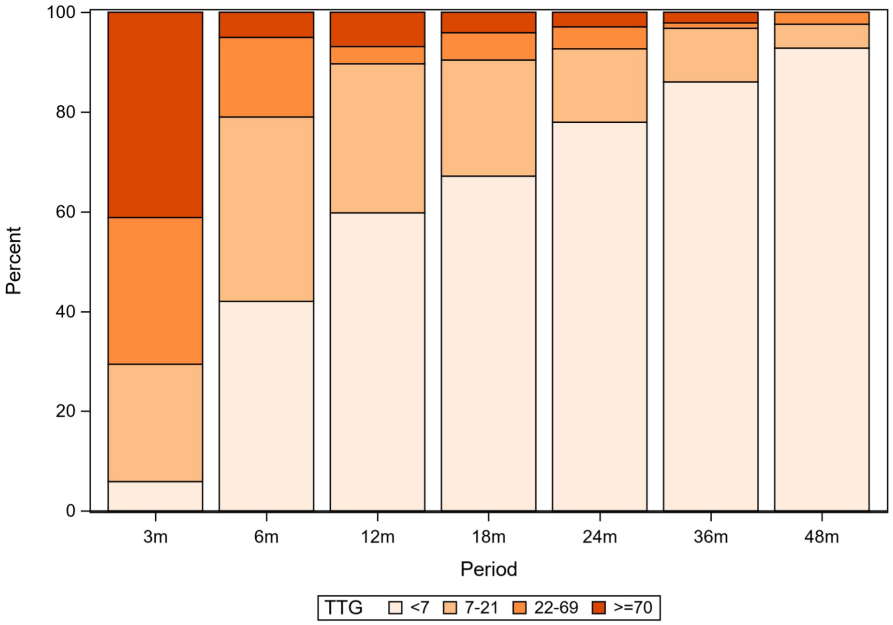


**FIGURE 3** The proportion of patients with normal tissue transglutaminase, <7 U/ml) by months since diagnosis of coeliac disease. Proportion of patients by tissue transglutaminase level category: <7 (normal), 7–21, 22–69, ≥70 U/ml. Data stratified by time-period (months) since coeliac disease diagnosis: 3 (test performed <3 months since diagnosis), 6 (3- < 9), 12 (9- < 15), 18 (16- < 21), 24 (21- < 30), 36 (30- > 42), and 48 (>42) months. Overall, 97 patients (59%) had a non-biopsy diagnosis based on repeated tissue transglutaminase measurements of ≥70 U/ml.

In our paediatric cohort, 14% were lost to follow up during childhood, meaning no coeliac disease-related consultation or tissue transglutaminase measurement over the past 24 months. Our rate of loss of follow up was lower than previously reported in children.[9,10] In 2019, Blansky et al. showed a 57% rate of loss of follow up in coeliac patients, defined as 18 months without follow up at a hospital-based paediatric gastroenterology unit.[10] An Israeli study from a paediatric gastroenterology unit found that 35% of patients with coeliac disease or potential coeliac disease had experienced loss of follow up, defined as no visit for coeliac disease or tissue transglutaminase measurement for the past 18 months.[9] However, one-third of the Israeli coeliac children who kept up a regular follow up had visited primary care physicians rather than hospital-based paediatric gastroenterologists.[9] Our data indicate that primary care physicians rarely conduct coeliac disease follow up.

There may be several explanations for the lower rate of loss of follow up in our study compared to previous works. First, the definition of loss of follow up varies. Motivated by European guidelines,[17] we defined loss of follow up as no coeliac disease-related visit or tissue transglutaminase test over the past 24 months in either hospital-based or general paediatric outpatient care. Previous studies have instead considered a shorter lag-period of 18-months and hospital-based paediatric gastroenterology care.[9,10] Some data also included potential coeliac disease,[9] a possible preclinical manifestation of coeliac disease,[11] where the need for long-term follow up of is less known, which may have affected the follow-up rate negatively. Second, in contrast to our study, previous estimates of loss of follow up have included the transition to adult care, a period that has been associated with loss of follow up for coeliac disease.[18]

We found no significant differences in socio-economic characteristics between patients who had a loss of follow up and those with continued follow up. This finding contrasts with the twofold risk of loss of follow up seen in US coeliac children with poor socioeconomic status.[10] We speculate that the apparent lack of a socioeconomic gradient in coeliac disease follow up of our study may be related to the universally accessible Swedish healthcare system,[19] where paediatric care is free, without individual co-payment, and excess costs for gluten-free food are partly reimbursed for most children <16 years of age.

This study included children living in an urban area of Sweden, a high-income country with a high prevalence of coeliac disease. The generalisability of our results to other countries requires further research. It is possible that the rate of loss of follow up differs for children in rural areas with a longer distance to care. Although age, sex, and year of diagnosis were broadly similar between children eligible for participation and those included in this study, our participants may still be more health conscious than the average coeliac patient. Hence, the 14% loss of follow-up rate in this cohort is likely a conservative estimate.

We found that dietary adherence and health-related quality of life were almost exclusively assessed through unstructured interviews, rather than validated questionaries. Unstructured interviews lack validity because each interview is unique. This result is consistent with a recent pan-European survey of coeliac disease follow up of mainly academic institutions.[8] In contrast to that study, our results suggest that laboratory testing beyond tissue transglutaminase is not routinely monitored during coeliac disease follow up. The difference in practice may be related to the lack of firm evidence on the benefits and harms of such monitoring in cases showing no indications of abnormalities at the time of diagnosis.[17] Our results of a tissue transglutaminase normalisation rate of 86% after 3 years of gluten-free diet align with previous paediatric results.[20]

Although physicians' experiences of paediatric coeliac disease care have recently been examined,[8,21] the patients' perspective has not been studied. Using a generic patient-reported experience

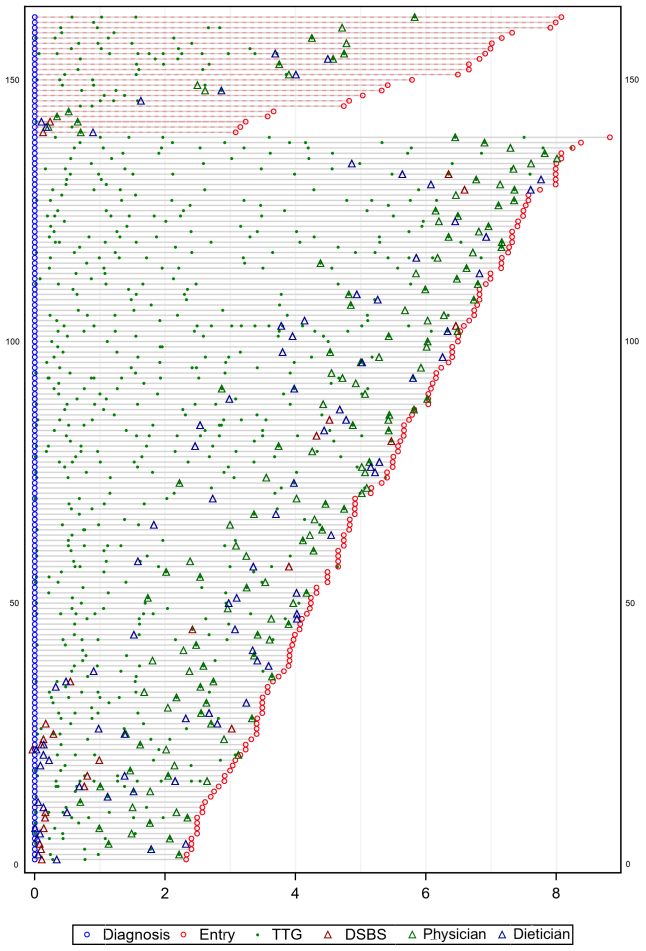


**FIGURE 4** Timing of tissue transglutaminase measurements and last coeliac follow-up visit in children with loss of follow up (top red dotted lines) and with continued follow up (bottom green lines). Each participant is represented by a horizontal line (red, crosshatched for loss of follow up), displaying tissue transglutaminase measurements (TTG, green dot) from the time of diagnosis (blue circle) until study enrolment (red circle). Patients are inversely ordered by duration since coeliac disease diagnosis. The last physician's visit at a paediatric outpatient clinic (since January 2019; green triangle) or Queen Silvia Children's Hospital (since diagnosis; QSCH, red triangle) is marked as well as the last dietician visit (blue triangle). Patient no. 24, for example, had performed seven tissue transglutaminase measurements, was last seen at a paediatric outpatient clinic and had no recorded dietician consultation.

measure questionnaire, the "overall impression" of coeliac care in this study scored 87 (95% CI = 84–90) on a scale from 0 to 100, with higher scores indicating better-reported care experience. Our result is consistent with patient-reported care experience from 60 Swedish hospital-based and general paediatric outpatient clinics in 2021, where the mean score of overall impression was 89 (range 84–96).[16] Of note, we found the lowest dimension score of 76 for influence over care, covering aspects of shared decision making, which motivates further research on these aspects of patient-centredcentred coeliac disease care.

### 4.1 | Strengths and limitations

This study is one of the first studies on the follow-up practice and rate of loss of follow up in children with coeliac disease. A strength of this study is the use of independently collected data from patient charts and laboratory records to define loss of follow up, which reduces the risk of spuriously defining loss of follow up merely because of a lack of data. Through comprehensive questionnaires, we could examine potential predictors for loss of follow up and its relationship to patient-reported experiences of coeliac disease care. Other strengths include efforts to assess and reduce self-selection bias and using uniform diagnostic criteria for coeliac disease.

A limitation of this study is the risk of type 2 error (i.e., erroneously accepting a false null hypothesis). The study sample size ($n$ = 162) and corresponding statistical power only allowed the ruling out of major differences between children with loss of follow up versus those with continued coeliac disease follow up. Due to internal attrition from incompletely answered questionaries, the number of participants included in some analyses was even lower. The proportion of and predictors for loss of follow up may be more evident with longer disease duration. Hence, the relative short follow-up period since coeliac disease, on average 5 years, may also have affected the risk of type 2 error in this study. We also acknowledge that erroneous recall of coeliac disease follow-up practice may have contributed to the risk of type 2 error. Finally, we did not include growth chart data and information on why specific patients underwent more extensive follow-up practice (e.g., laboratory work-up and control biopsy).

## 5 | CONCLUSION

In this regional cohort study of coeliac disease follow-up care one in seven patients had a loss of follow up during childhood. Loss of follow up was not linked to socio-economic characteristics of children with coeliac disease. Potential areas of care improvement include using validated gluten-free diet adherence and HRQoL questionnaires and an expanded role of dietician-led coeliac disease follow up. The chronic nature of coeliac disease warrants further research on its clinical follow up.

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### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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