The Rising Incidence of Celiac Disease in Scotland

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KEY WORDS
celiac disease, pediatric gastroenterology, epidemiology

ABBREVIATIONS
CD—celiac disease
CI—confidence interval
EIS—extraintestinal symptoms
ESPGHAN—European Society for Pediatric Gastroenterology, Hepatology and Nutrition
FH—family history
GI—gastrointestinal
IQR—interquartile range
MS—monosymptomatic
RHSC—Royal Hospital for Sick Children, Edinburgh
SIMD—standard index of multiple deprivation
T1DM—type 1 diabetes mellitus

Ms White drafted the initial manuscript, collected and interpreted the data, and carried out statistical analyses; Dr Merrick drafted the initial manuscript, and collected and interpreted the data; Dr Bannerman obtained funding, supervised the study, and reviewed and revised the manuscript; Drs Russell and Basude collected the data, and reviewed and revised the manuscript; Dr Henderson provided statistical support, interpreted the data, and reviewed and revised the manuscript; Drs Wilson and Gillett conceptualized and designed the study, obtained funding, supervised the study, were the guarantors for the cohort data, interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT’S KNOWN ON THIS SUBJECT: The overall incidence of pediatric celiac disease (CD) is rising, as are other autoimmune conditions. Additionally, increasing numbers of children are older at the point of diagnosis and are diagnosed with CD through active screening.

WHAT THIS STUDY ADDS: Accounting for screened and nonclassic cases, there is an independent 2.5-fold rise in the incidence of classically presenting cases of pediatric CD (Oslo definitions). Thus, indicating a true rise in pediatric CD incidence in southeast Scotland in 20 years.

abstract

BACKGROUND AND OBJECTIVES: Although the incidence of pediatric celiac disease (CD) is increasing globally, it is uncertain whether this is attributed to improved case ascertainment or signifies a true rise. We aimed to identify all incident cases of childhood CD in southeast Scotland over the period 1990 to 2009 to assess trends in total incidence and cases diagnosed as a result of (1) a classic presentation, (2) a nonclassic presentation, or (3) targeted screening.

METHODS: Twenty-year retrospective cohort study of case notes, pathology databases, endoscopy, and patient records for all children (<16 years of age) diagnosed with CD on biopsy in southeast Scotland (at-risk population of 225 000–233 000). Data were age-gender standardized and Poisson regression models used to calculate changes in incidence over time.

RESULTS: A total of 266 children were diagnosed from 1990 to 2009 with an increase in incidence from 1.8/100 000 (95% confidence interval [CI] 1.1–2.7) to 11.7/100 000 (95% CI 9.8–13.9) between the epochs 1990 to 1994 and 2005 to 2009, respectively (P < .0001). The incidence of nonclassic presentation (children with a monosymptomatic presentation and those with extraintestinal symptoms) and actively screened cases increased by 1566% (P < .05) and 1170% (P < .001) from 1990 to 1999 to 2000 to 2009, respectively. However, a rise in the incidence of Oslo classic cases from 1.51/100 000 (95% CI 0.91–2.38) in 1990 to 1994 to 5.22/100 000 (95% CI 3.98–6.75) in 2005 to 2009 (P < .01) remained evident.

CONCLUSIONS: The incidence of pediatric CD increased 6.4-fold over the 20 years. This study demonstrates that this rise is significant for classic CD, indicating a true rise in the incidence of pediatric CD. Pediatrics 2013;132:1–8
Celiac disease (CD) is a multisystem immunologic disorder that is environmentally precipitated by exposure to gluten in individuals with genetic susceptibility. Classic CD presents before school age with gastrointestinal (GI) symptoms; however, it is increasingly recognized that GI symptoms may be absent. Clinical guidelines published in 2009 set out the most effective means of diagnosing CD. Active screening of children at increased risk of CD, for example those with a strong family history (FH) or coexisting type 1 diabetes mellitus (T1DM), is strongly advised, in addition to children presenting with specific extraintestinal symptoms (EIS), such as prolonged fatigue. Improved awareness of the heterogeneity of CD may affect incidence, as greater numbers are diagnosed because of a lower threshold to test.

No reports on the incidence of childhood CD in southeast Scotland have been published since 1986. A recent audit of children (<16 years, n = 69) diagnosed in Wales revealed a rising trend in pediatric CD incidence from a mean of 2.08/100,000 per year from 1981 to 1985 to 6.89/100,000 per year from 2001 to 2005. Similar trends have been observed in Europe and North America over comparable time periods. A number of articles also report that a greater proportion of children in more recent years are diagnosed through targeted screening and experience fewer GI symptoms. However, no report has calculated the incidence of cases diagnosed over time because of a lower threshold to test or on the basis of the well-established classic presentation. Analyses performed on such robust data will help to determine whether a rise in incidence can entirely be attributed to a heightened clinical awareness or whether a true rise is evident.

We hypothesized that pediatric CD incidence had risen in southeast Scotland over the past 2 decades. We performed a retrospective cohort study of all newly diagnosed cases of childhood CD between 1990 and 2009, observing trends in total incidence and the incidence of cases diagnosed as a result of (1) classic presentation, (2) nonclassic presentation, and (3) targeted screening.

**METHODS**

The Royal Hospital for Sick Children (RHSC), Edinburgh, is the regional center for pediatric gastroenterology services in southeast Scotland, providing coverage for ~225,000 children younger than 16 years. Confirmatory small bowel biopsies have been performed at RHSC since the first use of jejunal capsule biopsies for diagnosis of CD, now superseded by endoscopic duodenal biopsy. Pediatric patients with symptoms suggestive of CD and/or positive serology are referred from the 3 regional district general hospitals, from clinicians in RHSC, and from general practitioners. Data on all incident cases of pediatric CD (<16 years at the time of first positive biopsy) diagnosed in the southeast Scotland regional network from 1990 to 2009 were collated from all relevant potential sources to ensure complete accrual: (1) hospital records (patients with an International Classification of Diseases, 10th Revision, coding of CD), (2) pediatric pathology records, (3) regional clinical database, (4) regional serology database, and (5) the electronic hospital record. Case notes were retrieved and, using a standard pro forma, information was documented electronically (Microsoft Access 2010; Microsoft, Redmond, WA).

All children with a clinical label/diagnosis of CD were identified but only those children who were biopsy-positive according to the 1990 European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria were included in the analysis. Although more recent guidelines have been produced, 1990 guidelines were used in view of time frame of data capture. Children resident outside of the 3 main southeast Scotland referral health boards were excluded from the final incidence figures to link with robust population data from the General Register Office for Scotland.11

**Data Collected**

Serology (antitransglutaminase, antiendomysial antibodies, and/or anti-gliadin antibodies) and duodenal biopsy pathology reports (Marsh-Oberhuber graded) were collected, enabling referencing to 1990 ESPGHAN diagnostic criteria. Demographic details at diagnosis, including age, gender, and postcode, were collected. Cases were subclassified as <2 years or ≥2 years. Using readily available government data, the deprivation level of each postcode was identified, known as the Standard Index of Multiple Deprivation (SIMD), a decile range from 1 to 10 (where 1 represents most deprived). Additionally, each postcode’s Urban-Rural classification code was determined (ranging from 1: “large urban area” to 6: “remote rural area”). However, not all postcodes are necessarily represented in the General Register Office for Scotland dataset (enabling linkage to SIMD and Urban-Rural data). Cases were initially split into 3 groups according to primary reason for testing: (1) actively screened (tested due to an “at-risk” condition or FH of CD in a first-degree relative); (2) “classic” (presenting with =2 GI symptoms or 1 GI symptom and additional common signs/symptoms of CD, for example fatigue or iron deficiency anemia); and (3) “nonclassic” (presenting with either 1 isolated GI symptom or extraintestinal indicators only). In the February 2012 review article in which CD and related terms were accurately defined (referred to as “Oslo” definitions).16 Ludvigsson
et al. defined pediatric classic CD as having signs and symptoms specifically of malabsorption, which in children is often characterized by failure to thrive, diarrhea, muscle wasting, poor appetite, and abdominal distension. To present results and discuss with reference to the most current terminology, our original classic group was further reclassified according to the Oslo criteria.

### Statistical Analyses

Data were separated into 4, 5-year epochs (1990–1994, 1995–1999, 2000–2004, 2005–2009) to compare time periods (hereafter referred to as epochs 1, 2, 3, and 4, respectively). Incidence rates for each 5-year epoch were age and gender standardized to enable valid analysis between cohorts. Southeast Scotland has witnessed a decline in the number of children <16 years of age from a mean of 230,587 per year in epoch 1 to 224,750 per year in epoch 4. Rates were therefore standardized to the 2001 Scottish Census population (the most recent complete census data available) to control for such changes. The direct method was used to adjust incidence figures. Ninety-five percent confidence intervals (95% CIs) were determined based on the methods described by Fay and Feuer. Children were split into 3 age groups: preschool (0–5 years), primary school (6–10 years), and secondary school (11–15 years) to enable standardization. Rates for each 5-year epoch are presented per 100,000 of the childhood population at risk (<16 years) (Table 1).

Poisson regression analyses were performed by using the epitools package in R v. 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria) to observe trends in the incidence of pediatric CD over time and trends in the incidence of cases diagnosed on the basis of classic symptoms, nonclassic symptoms, and active screening. Mann-Whitney, Kruskal-Wallis, and $\chi^2$ tests were performed as appropriate by using SPSS 18.0 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). Statistical significance was defined as a 2-tailed $P$ value <.05. This retrospective cohort study did not require ethical approval from the research ethics committee.

### RESULTS

#### Crude Numbers Diagnosed

In total, 290 children were diagnosed and treated for CD between 1990 and 2009 in southeast Scotland. Twenty-four children were excluded from the final CD incidence data for the following reasons: (1) histopathology findings were not sufficient to meet the 1990 ESPGHAN criteria ($n = 20$); or (2) place of residence was outside of the 3 southeast Scotland health board areas ($n = 4$). Therefore, 266 biopsy-positive children were included in the data analysis. Table 1 outlines the crude number of patients diagnosed.

### Patient Demographics

General and epoch-specific patient demographics are shown in Table 2. Median SIMD decile scores and sixfold urban-rural classification indices of patients with CD were comparable to the general southeast Scotland population and similar across each epoch. The overall male-to-female ratio was 1.0:1.6 and gender ratios were similar across all 4 time periods. Age (median; interquartile range [IQR]) at diagnosis rose significantly from epoch 1 to epoch 4 (Fig 1) and children presenting classically were younger at diagnosis (61 months; IQR 26–113) compared with the nonclassic and actively screened groups combined (109 months; IQR 67–141) ($P < .0001$). Furthermore, classic cases were significantly younger in epoch 1 (26 months; IQR 16–53) compared with epoch 4 (81 months; IQR 48.3–120.8) ($P < .0001$). A significantly greater proportion of children were <2 years of age at diagnosis in epoch 1 in comparison with epoch 3 and epoch 4 ($P < .01$ and $P < .0001$, respectively); and also in epoch 2 compared with epoch 3 ($P < .01$) and epoch 4 ($P < .0001$).

#### The Incidence of Pediatric CD in Southeast Scotland Is Rising

An increase in the age-gender standardized incidence of pediatric CD was observed over time, rising from 1.60/100,000 per year (95% CI 0.97–2.49) in epoch 1, to 3.81/100,000 per year (95% CI 2.79–5.10), 5.89/100,000 per year (95% CI 4.58–7.47), and 11.81/100,000 per year (95% CI 9.88–14.01) in epochs 2, 3, and 4, respectively. There was a significant rise in adjusted incidence figures between epoch 1 and each consecutive epoch ($P < .05$) (Fig 2), with a 638% rise observed from the earliest to the latest epoch. Although rates were similar for epochs 2 and 3 ($P < .05$), numbers rose from epoch 3 to epoch 4 ($P < .01$) (Fig 2).

### All Presentations of Pediatric CD Have Risen in Southeast Scotland

#### Actively Screened Cases

Just 1 child diagnosed in epoch 1 was actively screened for CD (due to FH in

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**TABLE 1** Crude Number of Pediatric CD Cases Diagnosed in Each Southeast Scotland Epoch by Gender (1990–2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Persons at Riska</th>
<th>Crude No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>1995–1999 (Epoch 2)</td>
<td>235,119</td>
<td>17</td>
</tr>
<tr>
<td>2000–2004 (Epoch 3)</td>
<td>230,116</td>
<td>25</td>
</tr>
<tr>
<td>2005–2009 (Epoch 4)</td>
<td>224,750</td>
<td>52</td>
</tr>
</tbody>
</table>

a Mean number of persons at risk (<16 y) for each year of the epoch (calculated from Scottish government midyear estimates).
a first-degree relative). A further 3 children were diagnosed through targeted screening in epoch 2 (2 FH, 1 T1DM), rising to 15 in epoch 3 (3 FH, 12 T1DM, 1 Down syndrome), and 30 children in epoch 4 (11 FH, 16 T1DM, 2 Down syndrome). Fifty-one percent (25/49) of children actively screened were completely asymptomatic. Because so few children were diagnosed through targeted screening in epoch 1, incidence rates were compared between epochs 1 and 2 combined and epochs 3 and 4 combined, rather than between each epoch. There was a significant 11-fold rise in the incidence of cases diagnosed through active screening from the 1990 to 1999 cohort (0.17/100 000 per year; 95% CI 0.05–0.45) to the 2000 to 2009 cohort (1.99/100 000 per year; 95% CI 1.45–2.69) (P < .0001) (Fig 3).

Nonclassic Cases

Thirty-eight children were diagnosed on the basis of a nonclassic presentation; none in epoch 1, 2 children in epoch 2 (1 presented with EIS and 1 presented monosymptomatically [MS]), 8 children in epoch 3 (4 EIS, 4 MS), rising to 28 cases in epoch 4 (13 EIS, 15 MS). Again, regression analysis was performed between the first and last 10 years of data collection. After age-gender standardization, the incidence rates of nonclassic cases rose significantly from 0.09/100 000 per year (95% CI 0.01–0.32) in the 1990 to 1999 cohort, to 1.41/100 000 per year (95% CI 0.97–2.00) (P < .05) in the cohort 2000 to 2009 (Fig 3).

Classic Cases

Nineteen of the 20 children captured in epoch 1 were diagnosed with a classic presentation, 41 classic cases in epoch 2, 45 in epoch 3, and 74 in epoch 4. Adjusted mean incidence rates were 1.51/100 000 per year (95% CI 0.91–2.38), 3.38/100 000 per year (95% CI 2.43–4.60), 4.07/100 000 per year (95% CI 2.99–5.41), and 6.77/100 000 per year (95% CI 5.35–8.48) in epochs 1, 2, 3, and 4, respectively. Although there was not a significant change in incidence between epochs 1 and 2, epochs 2 and 3, or epochs 3 and 4 (Supplemental Table 3), there was a significant rising trend in the adjusted number of classic cases from epoch 1 to epoch 3 (P < .05) and a significant fourfold rise in incidence was observed from epoch 1 to epoch 4 (P < .01) (Fig 4).

The numbers of children meeting the stricter Oslo classic presentation of CD were 20 in epoch 1, 41 in epoch 2, 43 in epoch 3, and 59 in epoch 4. After exclusion of children presenting with our own definition of classic presentation but without meeting the stricter Oslo classic presentation of CD, there was still a significant 2.5-fold rise in the incidence of Oslo classic cases between epoch 1 (1.51/100 000 year; 95% CI 0.97–2.38) and epoch 4 (5.22/100 000 per year; 95% CI 3.98–6.75) (Fig 4).
DISCUSSION

As hypothesized, a rise in incident pediatric CD was seen over a 20-year period in southeast Scotland, with a dramatic 6.4-fold increase between the epochs 1990 to 1994 and 2005 to 2009. Although similar trends have been reported in other European countries and North America, we uniquely show that approximately half the rise in the current cohort was attributed to children presenting with the strict Oslo classification of classic symptoms. This significant rise is independent of cases diagnosed through targeted screening or detected on the basis of nonclassic presentation, thus indicating a true rise in the incidence of pediatric CD.

To our knowledge, this is the largest dataset of pediatric CD in the United Kingdom. The use of age-gender standardization and Poisson regression models to detect true trends in CD incidence over time is unique and the extraction of data from multiple sources to enable cross-checking of information has resulted in the most complete data set possible. It is possible that children may have been diagnosed in adult services (although we expect these numbers to be minimal), inferring that the already significant accrual could be underestimated. Another possibility is that documentation of symptoms in the clinical notes may have been incomplete (eg, only 1 major symptom noted), and this is a potential limitation of our study when classifying according to number of symptoms. We hope, however, to have controlled for this at least in part by further defining classic cases according to the Oslo criteria, in which a single major symptom is sufficient.

This is the first study, to our knowledge, providing evidence for a true rise in the incidence of Oslo classic CD. The increase in childhood incidence we demonstrate is comparable to that shown by McGowan et al in Southern Alberta from 1990 to 2006. Incidence in epoch 4 is also comparable to that reported in Finland (12.3/100 000) but still much lower than that in Sweden (44/100 000). Buchanan et al observed a similar rise in numbers in the west of Scotland from 1995 to 2008. Therefore, we suspect that the rising trend in incidence applies to Scotland as a whole; however, we cannot be certain that this is the case in relation to classic cases. Our group has recently published prospective Scotland-wide incidence data over 1 year (2009/2010), but unfortunately there is no preceding data for comparison; it will be important to continue this project for accurate estimation of changes in incidence across Scotland. A number of population screening studies appear to show a rising prevalence of CD. In the United States, anti-tissue

**FIGURE 2**
Mean pediatric CD incidence between 1990 and 2009 (5-year epochs) in southeast Scotland. *P < .05; **P < .01; NS, not significant. P values determined from Poisson regression analysis.

**FIGURE 3**
Percentage rise in age-gender standardized incidence rates of cases diagnosed through active screening and due to nonclassic presentations over time. *P < .05, †P < .001. P values determined from Poisson regression analysis.
transglutaminase assays were performed on the frozen sera of 9133 young men from a historical cohort (1948–1954) and compared with 7210 similarly aged men from 2006 to 2008.23 Prevalence increased from 0.2% to 0.9%. A limitation, however, was that the historical group was composed of individuals originating from varying regions of the United States. Similarly, Finnish researchers revealed almost a 200% rise in the seroprevalence of adult CD from 1.03% in 1978 to 1980 to 1.99% in 2000 to 2001.24 However, it is not certain in either study how many were true cases because biopsies to confirm diagnosis were not performed.

Other immune conditions, including multiple sclerosis, T1DM, inflammatory bowel disease, and asthma, have also demonstrated a rise in frequency, with a significant and ongoing rise in incidence of pediatric-onset inflammatory bowel disease in Scotland demonstrated over the past 40 years.25,26 A decrease in the incidence of childhood infections has been noted over a matched time period in developed countries; the hygiene hypothesis proposes that early childhood infections are protective and therefore may account for the rise in immune disease.25

Geographical deprivation levels and urban/rural setting may affect the risk of infection; however, we found no difference between SIMD and urban/rural indices in children with CD and the general population. Factors such as family size and antibiotic use may be additional stimuli for an altered hygienic environment. This, however, cannot be the whole story in CD; gene-environmental interactions or epigenetic changes occurring in response to fetal/postnatal environment may have contributed to the rising trend, as genetic mutation alone cannot explain such rapid changes. For example, activation of interleukin-15 has long been described as a necessary step in the development of CD in genetically susceptible individuals.27 Proposed mechanisms for this are specific infectious agents, such as adenovirus, acting as a trigger, or the introduction of gliadin itself to the gut.28

Infant feeding practices have been implicated in CD development.10,29,30 A meta-analysis revealed a 52% reduction in CD risk in children breastfed at time of gluten introduction compared with those not breastfed at this time.30 It is hypothesized that immune mediating factors in breast milk, such as immunoglobulin A antibodies, lactoferrin, and lysozyme, may protect against GI infections that could play a role in the increased gut permeability in CD.31 Additionally, a small amount of gluten is present in breast milk, which could induce infant tolerance to gluten.51 On the other hand, a large prospective study found children exposed to gluten in the first 3 months of life (ie, introduction of weaning) had a fivefold increased risk of CD, compared with those exposed at 4 to 6 months (hazard ratio 5.17, 95% CI 1.44–18.57).30 There has been a shift toward later introduction of solid foods in Scotland, however, with 91% of mothers introducing solids by 4 months in 1995 compared with 60% in 2005,52 potentially contradicting hypotheses of protective effects. Statistics on breastfeeding at time of gluten introduction are unavailable.

Mode of delivery at birth has further been proposed to affect CD risk.33,34 Prospective data from 1969 to 2008 in the United States found a small increased risk in children after elective cesarean delivery controlling for maternal age, parity, maternal diabetes, maternal CD, and educational level (odds ratio 1.15, 95% CI 1.04–1.26).33 Microbial exposures in the birth canal could play a role in initial bowel colonization, and lack of exposure may impact immune response and mucosal barrier function.33 Combined emergency and elective cesarean rates increased by 78% between 1990 and 2010 in Scotland.35

Rising age at diagnosis has been observed in the United Kingdom since the 1960s,36 increasing to between 7 and 9 years more recently8,9,20 which is evident in the current dataset. Children presenting nonclassically and those identified through targeted screening were significantly older at diagnosis, with these phenotypes becoming more prolific as clinical awareness has improved. The rise in the age of classic

![Image](https://example.com/image.png)

**FIGURE 4**
Percentage rise in age-gender standardized incidence rates of cases diagnosed due to classic presentations and Oslo classic presentations of CD over time. *P < .01. P values determined from Poisson regression analysis.
cases is of interest. It is possible that the classic cases in epoch 4 have more subtle histopathological changes than those in epoch 1; testing this theory will require independent analysis and grading of all biopsies by an experienced pathologist. Additionally, over the period of our study there has been a trend toward positive net migration from overseas in the Scottish population as a whole. However, for the 0 to 16 age group, net migration is minimal; within this group, the lowest number of migrants are in the 10 to 16 age group. As such, we do not think this will have significantly influenced the rise in older classic cases.

Although a lower threshold to test has likely contributed to the rising trend in incidence observed, we must continue improving the diagnostic process. If the pediatric prevalence of 1% shown in some UK screening studies is accurate, it can be estimated that ~2300 children will have CD in southeast Scotland, yet the clinically diagnosed prevalence of pediatric (<16 years) CD in southeast Scotland at the end of 2004 was just 0.05% of the childhood population. Although the incidence of childhood CD in the region approximately doubled from the epoch 2000 to 2004 to the epoch 2005 to 2009, this still equates to a diagnosed prevalence of only ∼0.1%. Testing children with a working diagnosis of irritable bowel syndrome (who frequently present with nonclassic symptoms) could help to uncover more cases; a subset has been shown to have undiagnosed CD in published screening studies. However, there is no evidence to suggest that asymptomatic individuals are at higher risk of mortality compared with the general population and articles have demonstrated conflicting evidence as to whether diagnosing asymptomatic cases increases quality of life in the long term. Mass screening should not be implemented until it can be economically and ethically justifiable.

CONCLUSIONS

This cohort study demonstrates a significant rise in the incidence of pediatric CD in southeast Scotland from 1990 to 2009. The significant increase in classic cases is strongly suggestive of a true rise in CD incidence. Use of the strictest definition of classic pediatric CD does not abolish this significant rise. A rise in age at diagnosis may in part be accounted for by the introduction of screening and a lower threshold to test in nonclassic cases (since older children are more likely to present this way). However, a significant rise in age is demonstrated in classic cases alone. This may be suggestive of a change in disease pathogenesis itself. A large-scale prospective study is needed to investigate the role of the many potential exogenous factors in the development of pediatric CD.

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