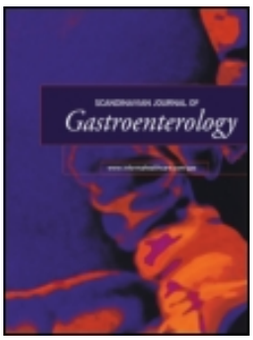

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ORIGINAL ARTICLE

An excess of prior irritable bowel syndrome diagnoses or treatments in Celiac disease: evidence of diagnostic delay

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Abstract

Objective. It is recognized that celiac disease can present with symptoms characteristic of irritable bowel syndrome (IBS) and that a substantial proportion of patients referred to gastroenterologists with these symptoms may have celiac disease. The authors set out to discover how commonly those suffering with celiac disease are misdiagnosed as suffering from IBS and whether such misdiagnosis delays the correct diagnosis. ***Materials and methods.*** A case control study using computerized records from the General Practice Research Database was conducted. The authors compared the proportion of patients with celiac disease who had a diagnosis of or had undergone treatment for IBS over a variety of time periods before the diagnosis of celiac disease with the proportion of a matched group without celiac disease who were similarly diagnosed or treated. ***Results.*** It was found that 16% of celiac patients had such a prior diagnosis compared to 4.9% of controls (a threefold increased risk of prior IBS; OR = 3.8, 95% CI: 3.6–4.2), and that if one looked at typical treatment for IBS rather than diagnostic codes, 28% of celiac patients appeared to have been treated compared to 9% of controls. Many of the diagnoses of IBS occurred within the last year before diagnosis of celiac disease, but there was a clear excess of IBS even 10 years earlier. ***Conclusions.*** In contemporary UK practice, it is likely that at least some patients with celiac disease spend many years being treated as having IBS. Following guidelines to test serologically for celiac disease will minimize this problem.

Key Words: *case control study, celiac disease, epidemiology, irritable bowel syndrome, misdiagnosis*

Introduction

We have known for some years that patients presenting to secondary care with symptoms typical of irritable bowel syndrome (IBS) may have celiac disease [1]. This is perhaps unsurprising given the overlap in symptoms between the two conditions. Throughout the last 50 years it has been repeatedly shown that those patients with celiac disease who present with symptoms typical of IBS can experience delays in the diagnosis of their celiac disease [2–7], yet this seems to remain a problem even in contemporary practice [8]. For inflammatory bowel disease and colorectal cancer, we have some idea of the degree to which misdiagnosis of the type suggested by these facts occurs in the general population (as opposed to a specialist clinic) [9]. What is not known, however, is to what extent the diagnosis of celiac disease is missed and one of IBS made in its place, or the difference in the proportion of individuals with IBS among those with celiac disease when compared to what we might expect in the generality of the population who do not have celiac disease. Nor is it entirely clear how great may be the delays between the potentially erroneous diagnosis of IBS and the correct diagnosis of celiac disease. Since celiac disease can now be diagnosed with relative ease, if guidelines are followed [10], it has a well recognized and highly successful therapy

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available, and an excellent prognosis when treated [11], the delay in this diagnosis may expose patients to unnecessary symptoms and risk of complications. We have, therefore, set out to establish the size of the problem of this misdiagnosis in routine clinical practice. To do this, we have conducted a case control study of incident celiac disease in the General Practice Research Database (GPRD), examining the presence of new diagnoses of IBS in the months and years before the diagnosis of celiac disease compared to general population controls who are similar in terms of their age and sex.

Methods

Design

A matched case control study was conducted to determine the differences in prior diagnoses of IBS between patients newly diagnosed with celiac disease and persons without celiac disease.

Setting

Data were extracted from the GPRD downloaded on January 2011. These data contain electronic information on consultations, diagnoses, and prescriptions delivered in primary care in the United Kingdom and have been validated for a wide variety of diagnoses [12]. We used GPRD data from 1987 to October 2010 accessed under the University of Nottingham's GPRD license. This dataset contains ~66 million person-years of available data for analysis among 11.26 million contributing patients within 613 general practices. Within the dataset, patients are labeled as "acceptable" for use in research if follow up is contiguous and data recorded does not raise worries about validity; data is also labeled as up-to-standard during the period for which an individual practice provided continuous data to a high standard defined by GPRD. This study was approved by the Independent Scientific Advisory Committee of the GPRD (protocol 11_047).

Study population

Incident cases of celiac disease were identified as acceptable patients with a first recording of celiac disease after the up-to-standard date of their practice or 1 year after their current registration date, whichever date was latest, and in whom the diagnosis was made after 16 years of age. The date of this first code for celiac disease is referred to as the date of diagnosis. Controls were selected from all acceptable patients with no record of celiac disease in their entire data. For each case, up to 10 controls were selected who matched the date of diagnosis, practice, sex, and age (±5 years), while selected controls, who had a gluten-free prescription at any time in their record, were subsequently dropped from the data set. Controls were assigned a date of pseudo-diagnosis equivalent to the date of diagnosis of their matched case.

Data extracted from GPRD records

For each subject we assessed age at date of diagnosis/pseudo-diagnosis and categorized this into 10-year-age bands. Records for all cases and controls were then examined for the presence of a code representing the diagnosis of IBS, and/or codes recording prescription of antispasmodic drugs typically used in the treatment of IBS (Mebeverine, Colpermin, or Alverine Citrate) prior to the date of diagnosis/pseudo-diagnosis. The first date for each of these two coding options was retained as the first evidence of a consultation for IBS-like symptoms in an individual.

The length of time before diagnosis/pseudo-diagnosis was categorized into 3-month intervals for the first year, then yearly intervals up to 10 years prior to diagnosis/pseudo-diagnosis.

Statistical analysis

For all cases of celiac disease, we present the proportion of cases and controls who had IBS recorded prior to the date of diagnosis of celiac disease/pseudo-diagnosis, overall and in the time periods specified above. These analyses are reported based purely on diagnostic codes for IBS, and by using a combination of a diagnostic and/or a prescription for antispasmodics typically used in IBS.

Results are then stratified by gender, by age, which is categorized into two groups (<50 years and 50+ years of age), and by the date of celiac disease diagnosis (before or after 1 January 2004 – to permit time for a change in behavior after IBS symptoms in celiac disease were publicized [1], while allowing adequate data to have accrued since for comparison). In all analyses, we present absolute number of cases and proportions with 95% confidence intervals (CI). We consider significant differences in proportions where confidence intervals are mutually exclusive. Odds ratios (OR) were derived by conditional logistic regression.

All analyses were conducted in Stata version 11 StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA.

Results

We identified 6826 adult incident cases of celiac disease and were able to match these to 61,850 controls

Table I. Demographical statistics.

	Case *n* (%) *n* = 6826	Control *n* (%) *n* = 61,850
Gender		
Male	2257 (33.1)	21,344 (34.5)
Female	4569 (66.9)	40,506 (65.5)
Age (years)		
16–19	207 (3)	1962 (3.2)
20–29	561 (8.2)	5137 (8.3)
30–39	991 (14.5)	9407 (15.2)
40–49	1415 (20.7)	13,077 (21.1)
50–59	1328 (19.5)	12,499 (20.2)
60–69	1244 (18.2)	10,666 (17.2)
70–79	778 (11.4)	6664 (10.8)
80+	302 (4.4)	2438 (3.9)

who had no evidence of celiac disease or gluten-free prescriptions. Cases were predominantly female (66.9%), and cases were most commonly diagnosed in the fifth decade of life (Table I).

When we examined for the presence of prior diagnoses of IBS, these were over three times as common in the celiac disease patients as in their controls (16% ever diagnosed vs. 4.9% - OR = 3.8, 95% CI: 3.6–4.2). Many of these excess diagnoses occurred in the year before the diagnosis of celiac disease (3.5% of cases had a new diagnosis of IBS in this time vs. 0.4% of controls); however, there was a statistically significant annual excess back as far as 10 years before diagnosis (Table II, Figure 1A).

When the definition of IBS was broadened to include prescriptions for antispasmodic drugs as well as diagnostic codes, this accentuated the above-described differences, suggesting as many as 28% of celiac disease patients might have been diagnosed or treated as having IBS prior to diagnosis compared to 9% of controls. Again, though most marked in the year before diagnosis, this discrepancy persisted many years before the diagnosis of IBS (Table II, Figure 1B). Repeating this analysis in only those subjects with at least 10 years of follow up yielded similar results (Table III, Figure 1C).

When analyses were stratified by sex, the absolute but not the relative excess of IBS diagnoses was higher in women, with a prior IBS diagnosis or therapy

Table II. Length of time between diagnosis of celiac disease and IBS using diagnostic codes with or without therapeutic codes.

		Case				Control			
	Prior diagnosis of IBS	*n* = 6826	%	CIs		*n* = 61,850	%	CIs	
IBS from diagnostic codes only	**Ever**	1095	16.04	15.17	16.91	3033	4.90	4.73	5.07
	Never	5731	83.96	83.09	84.83	58,817	95.10	94.93	95.27
	0–3 months	89	1.30	1.03	1.57	54	0.09	0.06	0.11
	3–6 months	67	0.98	0.75	1.22	52	0.08	0.06	0.11
	6–9 months	44	0.64	0.45	0.83	61	0.10	0.07	0.12
	9–12 months	40	0.59	0.40	0.77	61	0.10	0.07	0.12
	1–2 years	115	1.68	1.38	1.99	224	0.36	0.31	0.41
	2–3 years	77	1.13	0.88	1.38	225	0.36	0.32	0.41
	3–4 years	63	0.92	0.70	1.15	214	0.35	0.30	0.39
	4–5 years	61	0.89	0.67	1.12	213	0.34	0.30	0.39
	5–6 years	57	0.84	0.62	1.05	166	0.27	0.23	0.31
	6–7 years	51	0.75	0.54	0.95	170	0.27	0.23	0.32
	7–8 years	45	0.66	0.47	0.85	160	0.26	0.22	0.30
	8–9 years	41	0.60	0.42	0.78	159	0.26	0.22	0.30
	9–10 years	42	0.62	0.43	0.80	151	0.24	0.21	0.28
	10+ years	303	4.44	3.95	4.93	1123	1.82	1.71	1.92
IBS from diagnostic or prescription codes	**Ever**	1890	27.69	26.63	28.75	5701	9.22	8.99	9.45
	Never	4936	72.31	71.25	73.37	56,149	90.78	90.55	91.01
	0–3 months	167	2.45	2.08	2.81	131	0.21	0.18	0.25
	3–6 months	144	2.11	1.77	2.45	107	0.17	0.14	0.21
	6–9 months	81	1.19	0.93	1.44	130	0.21	0.17	0.25
	9–12 months	79	1.16	0.90	1.41	138	0.22	0.19	0.26
	1–2 years	202	2.96	2.56	3.36	495	0.80	0.73	0.87
	2–3 years	135	1.98	1.65	2.31	462	0.75	0.68	0.81
	3–4 years	112	1.64	1.34	1.94	438	0.71	0.64	0.77
	4–5 years	111	1.63	1.33	1.93	430	0.70	0.63	0.76
	5–6 years	101	1.48	1.19	1.77	395	0.64	0.58	0.70
	6–7 years	95	1.39	1.11	1.67	388	0.63	0.57	0.69
	7–8 years	89	1.30	1.03	1.57	301	0.49	0.43	0.54
	8–9 years	70	1.03	0.79	1.26	304	0.49	0.44	0.55
	9–10 years	71	1.04	0.80	1.28	282	0.46	0.40	0.51
	10+ years	433	6.34	5.77	6.92	1700	2.75	2.62	2.88

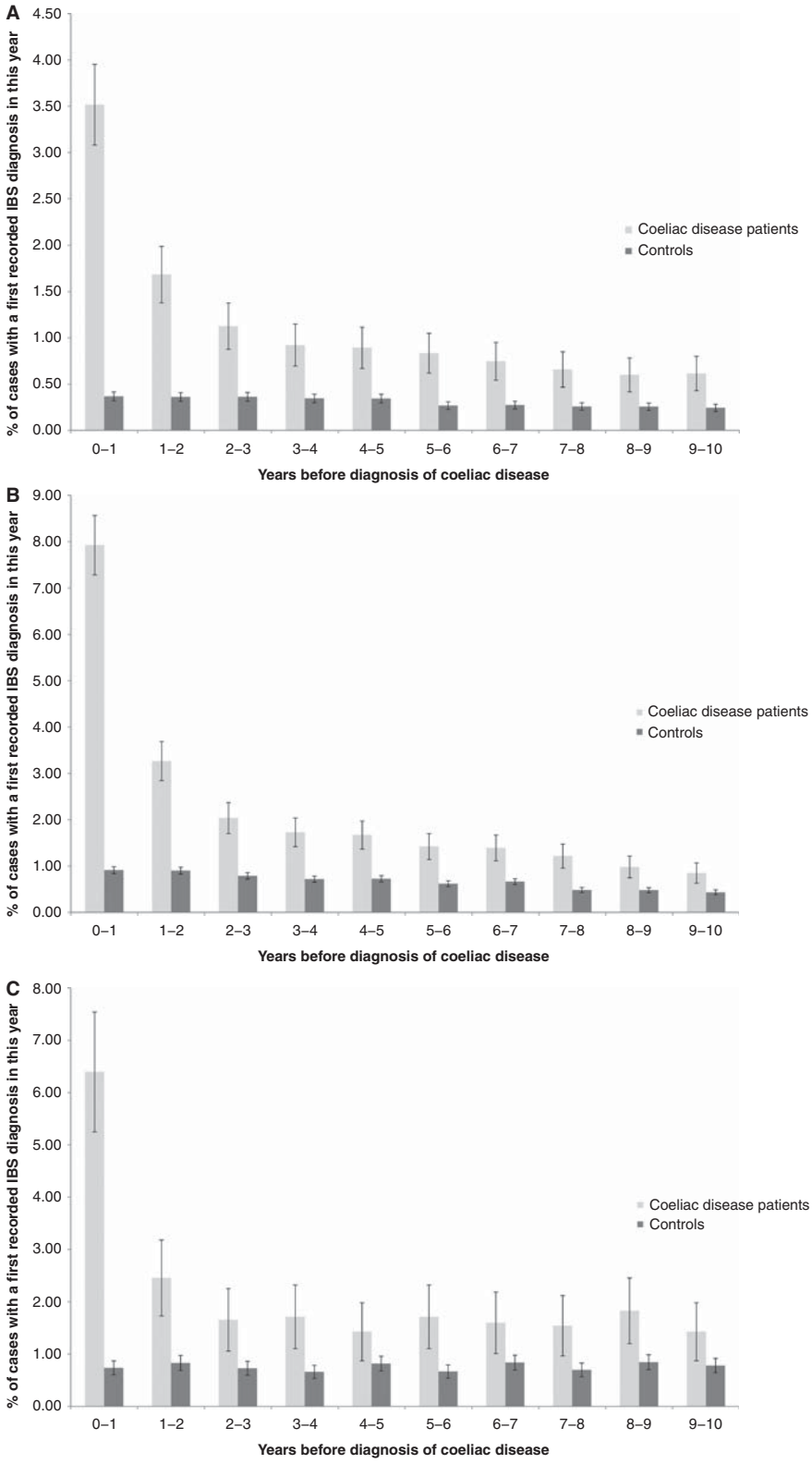

Figure 1. Proportion of subjects first recorded with IBS in years before diagnosis/pseudo-diagnosis of celiac disease. (A) All subjects using diagnostic codes only. (B) All subjects using diagnostic and treatment codes. (C) Only subjects with 10 or more years of data using diagnostic and treatment codes.

Table III. Length of time between diagnosis of celiac disease and IBS using diagnostic codes and therapeutic codes in patients with at least 10 years of follow up.

		Case				Control			
	Prior diagnosis of IBS	n = 1751	%	CIs		n = 15,753	%	CIs	
IBS from diagnostic or prescription codes only in those with >10 years follow up	**Ever**	547	31.24	29.07	33.41	1926	12.23	11.71	12.74
	Never	1204	68.76	66.59	70.93	13,827	87.77	87.26	88.29
	0–3 months	40	2.28	1.58	2.98	31	0.20	0.13	0.27
	3–6 months	33	1.88	1.25	2.52	13	0.08	0.04	0.13
	6–9 months	13	0.74	0.34	1.14	27	0.17	0.11	0.24
	9–12 months	13	0.74	0.34	1.14	29	0.18	0.12	0.25
	1–2 years	33	1.88	1.25	2.52	110	0.70	0.57	0.83
	2–3 years	24	1.37	0.83	1.92	106	0.67	0.55	0.80
	3–4 years	28	1.60	1.01	2.19	100	0.63	0.51	0.76
	4–5 years	23	1.31	0.78	1.85	123	0.78	0.64	0.92
	5–6 years	26	1.48	0.92	2.05	103	0.65	0.53	0.78
	6–7 years	26	1.48	0.92	2.05	121	0.77	0.63	0.90
	7–8 years	34	1.94	1.30	2.59	98	0.62	0.50	0.74
	8–9 years	29	1.66	1.06	2.25	119	0.76	0.62	0.89
	9–10 years	27	1.54	0.96	2.12	117	0.74	0.61	0.88
	10+ years	198	11.31	9.82	12.79	829	5.26	4.91	5.61

occurring in 31.8% of females and 19.4% of males with celiac disease compared to 11.4% of female and 5.2% of male controls. When stratified by age, the excess of IBS diagnoses was very similar in those over to those under 50 years of age with a prior diagnosis of IBS in 29.4% of those under 50 years of age and 26.2% of those over 50 among celiac disease cases compared to 9% of patients under 50 years and 9.4% of patients over 50 years among the controls. Our final stratification of the analysis by the date of celiac disease diagnosis showed a prior IBS diagnosis among 26.5% of cases diagnosed with celiac disease before 1 January 2004 and 28.6% of those diagnosed after that date, compared to figures of 7.1% and 10.8% for controls.

Discussion

Though it is inevitable that celiac disease and IBS will sometimes occur in the same individual, we have shown that there is a clear excess of IBS diagnoses and/or treatment for IBS in patients who will go on to be diagnosed with celiac disease compared to what might be expected in the general population. This is true for patients of both sexes, both young and old and has continued in the years, since it was widely publicized that many of those referred to secondary care with symptoms of IBS actually suffered from celiac disease. It is not possible to prove that these diagnoses of IBS represent misdiagnoses as we cannot retrospectively verify that celiac disease was (or was not) present at a time before it was actually diagnosed (i.e. around the time of the IBS diagnosis). That celiac disease was previously present is, however, the most obvious interpretation of our findings.

It is incumbent on us to consider two questions. First, we must ask ourselves whether it is likely that our results are correct, and second if they are correct, what their implications are. To answer the first question, we should consider the opportunities for error and bias in our work. Though the GPRD is known to provide diagnoses of high validity [12], there is potential for some error in the fact of the diagnoses we have relied on. We should consider, therefore, whether the specific diagnoses considered here (IBS and celiac disease) are valid. For celiac disease, a validation study has been conducted by requesting evidence of diagnoses from the general practitioners (G.P.s) of those coded with celiac disease [13] and the study demonstrated that in excess of 80% of those identified with celiac disease, via the definition we used in this paper, have good evidence to support this. For IBS, no such validation has occurred and in fact the possibility of errors has been demonstrated [9]. In the current study, however, since our intent is to suggest that some diagnoses of IBS in general practice may be invalid, we do not see this as a weakness, rather it is part of the study design. We must also consider the potential for error in the timing of the diagnoses we have used. If the "incident" cases of celiac disease we have studied were in truth prevalent, then the diagnosis of IBS may not predate them. However, based on the previous demonstration by Lewis et al. regarding the validity of the algorithm for identifying incident cases which we have used, we believe that this is unlikely to be a major problem [14]. We must also consider the possibilities of bias. Since the cases and controls were selected in an unbiased manner and their data prospectively collected for reasons unrelated to the study, neither selection nor recall bias

should have occurred. It is, however, possible that an ascertainment bias might act if IBS patients by dint of receiving more medical attention to gastrointestinal symptoms were rendered more likely to have otherwise asymptomatic celiac disease diagnosed. Since the greatest effect of such a mechanism would be likely to occur around the time of the initial diagnostic work up of a patient, this might well, at least in part, explain the excess of IBS diagnoses in the year before celiac disease diagnosis; however, it is harder to conceive as to how such a bias would act at earlier time points. Another potential bias in our analysis is due to the fact that we have not limited all analyses to patients with follow up throughout the time period studied. However, when we included only cases and controls who had at least 10 years of follow-up data and repeated our analyses in this restricted group (Table III and Figure 1C), the larger apparent excess of IBS diagnoses in this analysis suggests that, if anything, such a bias is causing us to underestimate the true size of the problem we are studying.

Also relevant to the assessment of the validity of our work is the manner in which it fits with preexisting knowledge since this study is by no means the first to examine the association between IBS and celiac disease [15]. Most studies that have examined the association have done so in a cross-sectional fashion by identifying people with IBS and looking for celiac disease among them via serology, biopsy, or both. Where findings in people with IBS have been compared to a control group a roughly three- to four-fold excess of celiac disease in the IBS group has been found [15]. Our overall OR reflects a very similar strength of association. Our study is, however, different in looking at prior IBS diagnoses among people with celiac disease. Of those few studies addressing this, most have been case series in which secondary or primary care records of people with celiac disease have been searched for prior evidence of IBS, much as we have done. Occasionally, the investigators asked people with celiac disease to complete a questionnaire [4]. The earliest of these studies were performed in the 1960s and they have sporadically continued until the present day [2,4,6,7]. Most show that symptoms or diagnoses of IBS are reported by patients and/or recorded by doctors many years before they were diagnosed with celiac disease, but only a couple of studies have attempted to quantify the excess diagnoses or symptoms of IBS among people later diagnosed with celiac disease as we have. In 1983, Gregory et al. sent a postal questionnaire to 40 people with celiac disease and 40 controls in and around Southampton, UK, to question about symptoms prior to diagnosis [4]. They found that nearly 50% of patients with celiac disease reported prior "abdominal discomfort" or "flatulence" compared to only about 5% of controls. Perhaps more relevant to our report is the study by Cannings-John et al. from Cardiff, Wales [16]. These investigators carried out a very similar study as our own, but instead of identifying cases in a large primary care database, they used cases identified in hospital and retrieved their primary care records for examination. They then recruited up to five controls from the general practice where the case originated from and examined their primary care records also. In their 68 cases and 160 controls, they found that IBS had been previously diagnosed in 16% and 7%, respectively, up to 5 years prior to diagnosis. The 9% excess of prior IBS diagnoses over the general population was remarkably similar to our own findings.

We believe, therefore, that our methodology is sound and our results coherent with the existing literature. What then do our results mean? If we accept that the excess IBS diagnoses do represent incorrect diagnoses and diagnostic delays, our results suggest that about 10% of celiac patients receive an incorrect diagnosis of IBS prior to receiving their diagnosis of celiac disease. Roughly one-third of these incorrect diagnoses occur in the year before a final diagnosis is made (and probably, therefore, do not represent appreciable delay in diagnosis), but the rest occur earlier, and a small subgroup (4.1% of all eventual celiac diagnoses) attract an erroneous diagnosis of IBS for their symptoms 5 or more years before the eventual identification of celiac disease as the cause of their problems. Our study is, in comparison to those that have come before it, far larger (~100 times bigger), more representative, and by definition more contemporary. Given this we have been able to show the precise variations in this delayed diagnosis by age, sex, and calendar period. Perhaps most surprisingly is the finding that even within the last 5–6 years, such misdiagnosis and subsequent delay in the diagnosis of celiac disease persists. Recent work by Norström et al. [17] suggests that such delay may cause an appreciable decrement in quality of life, yet this fact combined with our own findings should not lead to despondency. Though the diagnosis of celiac disease is easily missed [18], and our study suggests that it is missed in patients with symptoms suggestive of IBS, the diagnosis is now easily made. Recent guidance from the National Institute for Health and Clinical Excellence in England on the recognition and detection of celiac disease [11] has clearly stated that serological testing for celiac disease should be offered to children and adults with IBS. In separate guidance on the diagnosis and management of IBS in primary care [10], NICE recommend that in people who meet the IBS diagnostic criteria should undertake tests to exclude celiac disease, that is

antibody testing (endomysial antibodies or tissue transglutaminase). We believe our work strongly endorses the need for full implementation of these guidelines and also shows the opportunity to prevent unnecessary diagnostic delay of celiac disease in the future.

Acknowledgments

The study was conceived by Dr Card; all authors contributed to study design and planning. Dr Fleming carried out the analysis. All authors had access to the data and contributed to the interpretation. Drs Fleming and Card produced the first draft which was critically reviewed by all authors. All authors approved the final manuscript.

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