Table 1 Sociodemographic, clinical, and laboratory characteristics of the patients

	UC	IBS	HC
Patients (n)	22	24	23
Male:female	9:13	5:19	10:13
Age (years) (mean (SD))	41.2 (11.7)	45.9 (13.5)	38.2 (7.1)
Age range (years)	21 to 68	15 to 69	25 to 48
Endoscopic/histological inflammation (n)			
No	0	24	
Yes	22	0	
CRP (n <1 mg/dl) (mean (SD), range)	1.2 (1.4), 0 to 3.9	0.3 (0.3), 0 to 0.9	
Leucocytes (n <10) (mean (SD), range)	7.2 (1.8), 4.3 to 11.9	6.1 (1.2), 4.3 to 9.6	

CRP, C-reactive protein; HC, healthy controls; IBS, irritable bowel syndrome; UC, ulcerative colitis.

faecal levels of HBD-2 were significantly raised in patients with irritable bowel syndrome compared with healthy controls and were similar to those in the patients with ulcerative colitis. These results suggest activation of the mucosal innate defence system towards a proinflammatory response in patients with irritable bowel syndrome, in the absence of macroscopic signs of inflammation.

Inflammatory conditions of the gastrointestinal tract—including inflammatory bowel disease and acute gastrointestinal infections—are associated with disturbed intestinal motor function and decreased sensory thresholds.[6] These sensorimotor abnormalities are not necessarily related to an overt inflammatory reaction as they can occur even when inflammation is minimal and is restricted to the mucosa.[6] Thus altered sensory and motor function accompanied by the development of symptoms suggestive of irritable bowel syndrome has been observed in patients with quiescent ulcerative colitis.[7] First support for a possible involvement of intestinal inflammation in irritable bowel syndrome was based on observations of increased numbers of mast cells in the muscularis externa[8] or a significant increase in lamina propria immune cells in the colonic mucosa of affected patients,[9] and has been under discussion since. Nonetheless, the general consensus is that irritable bowel syndrome is a non-inflammatory disease.

In conclusion, this is the first study to present preliminary data on faecal HBD-2 levels in patients with irritable bowel syndrome, ulcerative colitis, and healthy controls. In contrast to our hypotheses, our findings support a proinflammatory response of the mucosal innate defence system in irritable bowel syndrome. The functional significance of these findings remains to be elucidated.

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References

1 **Wehkamp J**, Fellermann K, Herrlinger KR, *et al.* Human β-defensin 2 but not β-defensin 1 is expressed preferentially in colonic mucosa of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2002;**14**:745–52.
2 **Voss E**, Wehkamp J, Wehkamp K, *et al.* NOD2/CARD15 mediates induction of the antimicrobial peptide human beta-defensin-2. *J Biol Chem* 2006;**4**:2005–11.
3 **Harder J**, Bartels J, Christophers E, *et al.* A peptide antibiotic from human skin. *Nature* 1997;**387**:861.
4 **Wehkamp J**, Harder J, Wehkamp K, *et al.* NF-κB and AP-1-mediated induction of human β-defensin-2 in intestinal epithelial cells by Escherischia coli Nissle 1917: a novel effect of a probiotic bacterium. *Infect Immun* 2004;**10**:5750–8.
5 **Wehkamp J**, Harder J, Weichenthal M, *et al.* Inducible and constitutive β-defensins are differentially expressed in Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2003;**4**:215–23.
6 **Rao SS**, Read NW, Brown C, *et al.* Studies on the mechanism of bowel disturbance in ulcerative colitis. *Gastroenterology* 1987;**93**:934–40.
7 **Isgar B**, Harman M, Kaye MD, *et al.* Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983;**24**:190–2.
8 **Hiatt RB**, Katz L. Mast cells in inflammatory conditions of the gastrointestinal tract. *Am J Gastroenterol* 1962;**37**:541–5.
9 **O'Sullivan M**, Clayton N, Breslin NP, *et al.* Increased mast cells in the irritable bowel syndrome. *Neurogastroenterol Motil* 2000;**12**:449–57.

Is there an association between coeliac disease and irritable bowel syndrome?

We read with interest the study by van der Wouden *et al* (*Gut* 2007;**56**:444–5). The authors describe their experience of investigating patients with irritable bowel syndrome (IBS fulfilling the Rome II criteria) for coeliac disease. They tested 152 patients with IBS using IgA endomysial antibodies and total IgA level or duodenal biopsy; 36 patients were subsequently biopsied but there were no cases of coeliac disease diagnosed (prevalence 0%: 95% confidence interval, 0% to 4%). They concluded that the prevalence of coeliac disease in patients with IBS is low and that screening may be ineffective.

We feel cautious about accepting these results as definitive proof of no relation between these two common conditions. Their study has some methodological limitations. First, the referral pattern appears to be significantly different from that seen in the United Kingdom, with approximately 55 patients being assessed for IBS symptoms per year by three physicians. Does this suggest that IBS is not a condition commonly referred to secondary care in the Netherlands? Perhaps primary care physicians have already investigated patients for coeliac disease before referral? Second, assuming the accepted population prevalence for coeliac disease is 1%, then with a sample size of 152 (11 patients were not serologically tested or biopsied) there is only a 21.4% power to detect a threefold difference (assuming a significance level of 0.05). Thus this study is underpowered. Third, endomysial antibody (EMA) negative coeliac disease is well recognised. The use of EMA in isolation may lower the detection sensitivity and with only 22% of their patients (36/163) having a duodenal biopsy, it is possible that some cases of coeliac disease could have been missed. Fourth, importantly, there are several studies examining this issue (table 1), not all of which were cited by the authors in their report. These international studies suggest that the prevalence of coeliac disease in cohorts of patients with IBS is higher than in the general population.

Table 1 Studies of coeliac disease in cohorts of patients with irritable bowel syndrome

Report	Country	n	Setting	Criteria	Serology	Biopsy	Prevalence	Outcome
Sanders[1]	UK	300	Secondary care	Rome II	AGA, EMA	Yes	4.7%	Better on GFD
Sanders[2]	UK	123	Primary care	Rome II	AGA, EMA	Yes	3.3%	Better on GFD
Shahbazkhani[3]	Iran	105	Secondary care	Rome II	AGA, EMA	Yes	11.4%	Better on GFD
Fasano[4]	USA	5073	Mixed	Symptom group	AGA, EMA, TTG	Yes	Chronic diarrhoea (n=1848), 3.85% Abdominal pain (n=1695), 3.23% Constipation (n=1530), 2.6%	NR
Holt[5]	UK	138	Primary care	Rome I	AGA, EMA	No	0.7%	NR
Locke[6]	USA	50	Primary care	Manning	tTG	No	0%	NR
Hin[7]	UK	132	Primary care	NR	EMA	Yes	0%	NR
Catassi[8]	USA	22	Primary care	NR	EMA, tTG	Yes	31.8%	NR

AGA, antigliadin antibodies, EMA, endomysial antibodies; GFD, gluten-free diet; NR, not reported; tTG, tissue transglutaminase antibodies.

Furthermore, the association of coeliac disease and IBS symptoms is biologically plausible with many mechanisms being reported—for example, autonomic dysfunction, intussusception, exocrine pancreatic disease, small intestinal ulceration, and associated microscopic colitis. Our own group found an increased prevalence of coeliac disease in patients referred with surgical abdominal pain, notably in those with unexplained or non-specific abdominal pain.[9] The association between IBS and coeliac disease appears to operate in both directions, as patients with coeliac disease (on a gluten-free diet) may describe IBS symptoms.[10] Similarly, abdominal pain, diarrhoea, or constipation were associated with an increased risk of coeliac disease in a large multicentre study.[11] All of these symptoms can overlap with IBS.

From a clinical perspective, is investigating IBS patients for coeliac disease a valid approach? It is recognised that the majority of patients with coeliac disease have significant delays in diagnosis and once established on the gluten-free diet they derive symptomatic benefit. Case finding for coeliac disease in patients with IBS symptoms is both cost-effective and beneficial in terms of quality of life years gained, even at prevalence values of 1.1–2%.[12] We accept that further multicentre studies in both primary and secondary care are required to resolve this debate. In such studies assessment of quality of life and symptom resolution (when individuals are established on a gluten-free diet) is imperative. Despite the existing evidence, investigating for coeliac disease in patients fulfilling the Rome II criteria is still not widely accepted (although recommended in UK guidelines). Why should this be? Is this a clash of ideological dogma when considering possible mechanisms for IBS?

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References

1 **Sanders DS**, Carter MJ, Hurlstone DP, *et al.* Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet* 2001;**358**:1504–8.
2 **Sanders DS**, Patel D, Stephenson TJ, *et al.* A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* 2003;**15**:407–13.
3 **Shahbazkhani B**, Forootan M, Merat S, *et al.* Coeliac disease presenting with symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther* 2003;**18**:231–5.
4 **Fasano A**, Berti I, Gerarduzzi T, *et al.* Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;**163**:286–92.
5 **Holt R**, Darnley S, Kennedy T, *et al.* Screening for coeliac disease in patients with clinicla diagnosis of irritable syndrome. *Gastroenterology*. 2001;120: A757 [abstract 4064], (suppl 1).
6 **Locke GR**, Murray JA, Zinsmeister AR, *et al.* Celiac disease serology in irritable bowel syndrome and dyspepsia: a population-based case–control study. *Mayo Clin Proc* 2004;**79**:476–82.
7 **Hin H**, Bird G, Fisher P, *et al.* Coeliac disease in primary care: case finding study. *BMJ* 1999;**318**:164–7.
8 **Catassi C**, Kryszak D, Louis-Jacques O, *et al.* Detection of celiac disease in primary care: a multicenter case-finding study in North America. Am J Gastroenterol 2007;102, March 13 [Epub ahead of print]..
9 **Sanders DS**, Hopper AD, Azmy IA, *et al.* Association of adult celiac disease with surgical abdominal pain: a case–control study in patients referred to secondary care. *Ann Surg* 2005;**242**:201–7.
10 **O'Leary C**, Wieneke P, Buckley S, *et al.* Celiac disease and irritable bowel-type symptoms. *Am J Gastroenterol* 2002;**97**:1463–7.
11 **Fasano A**, Berti I, Gerarduzzi T, *et al.* Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;**163**:286–92.
12 **Mein SM**, Ladabaum U. Serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome: a cost effectiveness analysis. *Aliment Pharmacol Ther* 2004;**19**:1199–210.

Risk of pancreatic cancer in patients with cystic fibrosis

About 5–10% of pancreatic cancers have been linked to an underlying genetic disorder, usually inherited in an autosomal dominant manner. We have previously studied the risk of cancer in patients with cystic fibrosis and found that, although the overall risk of cancer was not increased, there was a fivefold increase in the risk of digestive tract cancer.[1 2] Because only four patients developed pancreatic cancer, it was difficult to estimate the risk accurately. Since the publication of these reports we have obtained information on additional patients with both cystic fibrosis and pancreatic cancer from the US cystic fibrosis patient registry, from published reports, and by querying surgeons, pathologists, and cystic fibrosis physicians in the USA, Canada, and Europe.

We now describe nine patients with cystic fibrosis and pancreatic cancer identified during the study period (1985 to 2006), including four from our original reports (table 1). Based on age, sex, race, and calendar-year-specific incidence rates obtained from the Surveillance, Epidemiology, and End Results (SEER) programme, we previously estimated the number of expected pancreatic cancers in the USA cystic fibrosis population (n = 28 858) for the 10 year period 1990 to 1999 to be 0.4.[2] Assuming that the cystic fibrosis population in Europe is approximately equal to that in the USA, then the expected number of pancreatic cancers in the combined USA and European populations during the period 1985 to 2005 is 1.7, yielding a risk ratio of 5.3 (95% confidence interval, 2.4 to 10.1).

There were four women and five men with a median age of 35 years (range 18 to 58). Five patients had known cystic fibrosis mutations: four were ΔF508 homozygotes and one was a ΔF508 heterozygote. Five patients had pancreatic exocrine insufficiency, five had mild or moderate lung disease, and two had potential risk factors that might have increased their risk of pancreatic cancer. One patient had received six years of immunosuppressive treatment following lung transplantation before developing pancreatic cancer; this patient had also received growth hormone for three years. Another patient developed pancreatic mucinous cystadenocarcinoma in a cyst that had been present for 13 years.

The increased relative risk of pancreatic cancer in the cystic fibrosis population compared with the general population is an age related finding: pancreatic cancer is rare in younger individuals. However, although we observed an excess risk of pancreatic cancer within the cystic fibrosis population compared with the background population, we were able to identify only nine patients in North America and Europe over a 21 year period. This translates into an incidence of approximately 1/100 000/year (nine pancreatic cancers in 1.2 million person-years). Therefore, although the

Table 1 Pancreatic cancer in cystic fibrosis patients

Report	Population, year of diagnosis of pancreatic cancer (type)	Patient characteristics	Remarks
Petrowsky[3]	Switzerland, 2005 (adenocarcinoma)	18 year old female, ΔF508/unknown; pancreas insufficient	Lung transplantation followed by immunosuppression ×6 years and growth hormone ×3 years before pancreatic adenocarcinoma
Oermann[4]	USA, 2004 (mucinous cystadenocarcinoma)	19 year old female, ΔF508/ΔF508; pancreas insufficient	Mucinous cystadenocarcinoma within cyst diagnosed at age 6
Davis[5]*	UK, 1985 (adenocarcinoma)	23 year old female, unknown genotype	Mild lung disease
McIntosh[6]*	USA, 1987	26 year old male, unknown genotype; diabetic pancreas insufficient	Moderate lung disease
Tummler	Germany, 2003	35 year old male, ΔF508/ΔF508; diabetic pancreas insufficient	Personal communication
Tsongalis[7]	USA, 1993 (adenocarcinoma)	39 year old male, ΔF508/ΔF508; pancreas insufficient	Mild lung disease
Tedesco[8]	USA, 1986	42 year old male, unknown genotype	Mild lung disease
Maisonneuve[2]	USA, 2000 (ductal adenocarcinoma)	49 year old female, ΔF508/ΔF508; diabetic	
Sheldon[9]*	UK, 1991 (carcinoma)	58 year old male, unknown genotype	Mild lung disease

*Also described in the report by Neglia.[1]