

Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population

M. T. HILLILÄ & M. A. FÄRKKILÄ

Department of Medicine, Division of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland

Accepted for publication 4 May 2004

SUMMARY

Background: Prevalence of irritable bowel syndrome shows great variation among epidemiological studies, which may be due to different diagnostic criteria.

Aim: To assess prevalence of irritable bowel syndrome according to various diagnostic criteria and to study differences in symptom severity, psychopathology, and use of health care resources between subjects fulfilling different diagnostic criteria.

Methods: A questionnaire was mailed to 5000 randomly selected adults. Presence of irritable bowel syndrome was assessed by four diagnostic criteria: Manning 2 (at least two Manning symptoms), Manning 3 (at least three Manning symptoms), Rome I and Rome II.

Results: Response rate was 73%. Prevalence of irritable bowel syndrome by Manning 2, Manning 3, Rome I and Rome II criteria was 16.2%, 9.7%, 5.6%, and 5.1% respectively. Of those fulfilling Rome II criteria, 97% fulfilled Manning 2. Severe or very severe abdominal pain was reported by 27–30% of Manning-positive subjects, and 44% of Rome-positives. Prevalence of depression in Manning 2, and Rome II groups was 30.6 and 39.3%.

Conclusions: Prevalence of irritable bowel syndrome by Rome II criteria is considerably lower than by Manning criteria. Subjects fulfilling Rome criteria form a subgroup of Manning-positive subjects with more severe abdominal symptoms, more psychopathology, and more frequent use of the health care system.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with abdominal pain, discomfort, and changes in bowel habit. Its prevalence ranges in population-based studies between 10 and 26% in western countries.¹ In a recent review of IBS in EU countries the prevalence was approximated as 10% of the adult population with an average cost of 1000 per patient year, leading to a total cost of 28.38 billion.²

The definition of IBS has changed over time. In 1978, Manning published the first symptom-based diagnostic criteria for IBS, which since then have been widely used

in epidemiological studies. According to Manning criteria, the more of the following six symptoms are present, the more likely the IBS diagnosis: looser stools at onset of pain, more frequent bowel movements at onset of pain, pain eased after bowel movement, abdominal distension, passage of mucus, or feeling of incomplete evacuation.³ No minimum number of these six symptoms was recommended, however, resulting in the use of various number of symptoms, usually two or three, to define IBS.^{4–7} In 1989, a working committee published new criteria for IBS diagnosis,⁸ criteria then revised and published in 1992 as the Rome criteria (later Rome I criteria).⁹ The newest definition and diagnostic criteria for IBS, the Rome II criteria, appeared in 1999.¹⁰

Our objectives were to assess the effect of diagnostic criteria on prevalence figures for IBS in a population-based setting and to evaluate whether the IBS groups

Correspondence to: Dr M. T. Hillilä, Department of Medicine, Division of Gastroenterology, Helsinki University Central Hospital, PL 340, FIN-00029 HUS, Helsinki, Finland.
E-mail: markku.hillila@hus.fi

detected differed in respect to demographic properties, severity of IBS symptoms, use of health care facilities, depression and anxiety.

MATERIALS AND METHODS

In 2001, there were 5.2 million residents in Finland. The main language is Finnish while 6% of Finns have Swedish as their native language. A computer-based random sample of 5000 Finnish residents aged 18–64 years came from the national population registry. The sample comprised 2490 men and 2510 women with Finnish as their native language. In September 2001, they each received a questionnaire with an explanatory letter and a stamped envelope for a reply. Two reminders were sent. The questionnaire included questions related to IBS and dyspepsia according to the Rome II Integrative Questionnaire, developed for epidemiological surveys.¹¹ After translating these items into Finnish the questionnaire was back-translated into English by a bilingual Finnish translator who was not aware of the original Rome II Integrative Questionnaire. The translation was then reviewed by a native American translator. Presence of IBS was assessed by four diagnostic criteria: (i) Manning 2 criteria (at least two of the six Manning symptoms); (ii) Manning 3 criteria (three or more of the Manning symptoms); (iii) Rome I criteria; and (iv) Rome II criteria (Table 1).

The questionnaire also included a Finnish modification of the 13-item Beck Depression Inventory.^{12, 13} The Finnish version (RBDI) has been developed for population-screening purposes.¹⁴ A positive-choice answer has been added to each item to measure self-confidence. The Finnish modification contains 14-items: 13 for depression and one for anxiety and it has shown good reliability and validity in screening the Finnish population.¹⁵ Depression is defined as mild at a score of 5–7, moderate, 8–15, and severe at 16 or more. Anxiety is defined as mild (score 1), moderate (score 2) or severe (score 3).

The questionnaire also covered basic demographic data, previous gastrointestinal diseases and symptoms, operations, medications, severity of IBS-symptoms if present, and factors worsening the symptoms. Abdominal pain and discomfort was assessed by a 4-grade Likert scale (mild, moderate, severe, very severe). Frequency of abdominal pain/discomfort was assessed by 5-grades (seldom or never, sometimes, often, very often, constantly).

Table 1. Manning, Rome I and Rome II criteria for irritable bowel syndrome (IBS)

Manning criteria for IBS
Looser stools at onset of pain
More frequent bowel movements at onset of pain
Pain eased after bowel movement
Visible (abdominal) distension
Passage of mucus
Feeling of incomplete evacuation
Rome I criteria for IBS
At least 3 months continuous or recurrent symptoms of
Abdominal pain or discomfort which is:
Relieved with defecation; and/or
Associated with a change in frequency of stool; and/or
Associated with a change in consistency of stool and
Two or more of the following, on at least a quarter of occasions or days
Altered stool frequency
Altered stool form (lumpy/hard or loose/watery)
Altered stool passage (straining or urgency, feeling of incomplete evacuation)
Passage of mucus
Bloating or feeling of abdominal distension
Rome II criteria for IBS
At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features
Relieved with defecation; and/or
Onset associated with a change in frequency of stool; and/or
Onset associated with a change in form (appearance) of stool
Symptoms cumulatively supporting IBS diagnosis
Abnormal stool frequency
Abnormal stool form (lumpy/hard or loose/watery stool)
Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
Passage of mucus
Bloating or feeling of abdominal distension

All questionnaires returned were scanned optically, and data was transformed into Excel-form for analysis.

STATISTICAL METHODS

Data were analysed with SPSS and NCSS software. Prevalence figures according to each diagnostic criteria were calculated with 95% confidence intervals (CI). Two variables were considered statistically different if their 95% CI did not overlap. Variables were analysed for associations with each diagnostic category by the chi-square test for categorical and *t*-test for dimensional variables. Concordance between the criteria was analysed with κ statistics. A κ -value of 0.0–0.2 indicates slight agreement, 0.2–0.4 fair agreement, 0.4–0.6 moderate agreement, and 0.6–0.8 substantial

agreement; a κ -value of 0.8–1.0 indicates near perfect agreement.¹⁶

RESULTS

The random sample included 5000 subjects. The postal service reported 22 unknown addresses and returned those letters. After two reminders, the response rate was 73.0%, higher among females (78.9%) than males (67.0%). Mean age of respondents was 42.1 years (95% CI: 41.6–42.5) with the male-to-female ratio of 45.1/54.9%. Non-respondents were younger than respondents, with a mean age of 38.7 years (95% CI: 37.3–39.0). The oldest age group (55–65 years) showed no statistically significant difference in response rate by gender. In all the other age groups, females were more likely to respond than males (Table 2).

Prevalence of IBS

Altogether 600 respondents (16.5%) fulfilled at least one of the IBS criteria. The prevalence of IBS according to Manning 2, Manning 3, Rome I, and Rome II criteria was 16.2%, 9.7%, 5.6%, and 5.1%, respectively. IBS was more common among females based on either of the Manning criteria, while Rome I and Rome II criteria revealed no differences in gender distribution. No statistically significant differences appeared between prevalences of IBS among age groups for any of the criteria applied (Table 3).

Overlap among diagnostic criteria is shown in Figure 1. Of the 600 subjects meeting any IBS criteria, 587 (97.8%) also met Manning 2 criteria. One hundred and seventy-nine subjects (97.3%) of the Rome II group also met Manning 2 criteria, and 153 (83.2%) of the Rome II group also met Rome I criteria. Only four

Table 2. Response rate (%)

Age (years)	Male	Female	Total	P* value
18–24	53.5	73.5	63.3	<0.000
25–34	67.1	76.2	71.6	0.002
35–44	62.6	78.7	70.6	<0.000
45–54	69.5	79.5	74.6	<0.000
55–65	81.1	85.0	83.1	0.124
Total	67.0	78.9	73.0	

* Male vs. female.

subjects (2.2%) in the Rome II group met no IBS definition other than Rome II. Both Manning 2 and Manning 3 criteria showed a moderate agreement with Rome II, with κ -values of 0.42 and 0.52, respectively. Their agreement with Rome I criteria was slightly better, with respective κ -values of 0.45 and 0.53. However, Rome I and Rome II criteria showed a substantial agreement, with a κ -value of 0.78.

Demographics

No significant difference existed in age distribution or marital status between those meeting an IBS criterion and controls. The lowest educational level was less frequent among respondents fulfilling either of the Manning criteria. On the contrary, Rome I- and Rome II-positive groups showed a tendency towards a lower percentage at the highest educational level (high-school graduate). Those who met three Manning-symptom criteria more frequently worked irregular hours than did those not meeting Manning 3 criteria. Among Manning 2, Rome I or Rome II groups, there appeared a tendency towards over-representation of irregular working hours, although this failed to reach statistical significance (Table 4).

Table 3. Prevalence of irritable bowel syndrome (IBS) according to different diagnostic criteria and age (%;95% CI)

	Manning 2 (n = 587)	Manning 3 (n = 353)	Rome I (n = 204)	Rome II (n = 184)
Total IBS prevalence (n = 3631)	16.2 (15.0–17.4)	9.7 (8.8–10.7)	5.5 (4.8–6.3)	5.1 (4.4–5.8)
Male	13.1 (11.4–14.8)	8.3 (7.0–9.7)	5.1 (4.0–6.2)	5.1 (4.0–6.2)
Female	19.2 (17.4–20.9)	11.2 (9.8–12.6)	6.1 (5.0–7.2)	5.3 (4.3–6.3)
Age				
18–24 (n = 416)	17.8 (14.1–21.5)	10.3 (7.4–13.3)	6.0 (3.9–8.8)	5.3 (3.3–7.9)
25–34 (n = 683)	17.4 (14.6–20.3)	10.5 (8.2–12.8)	5.3 (3.7–7.2)	5.3 (3.7–7.2)
35–44 (n = 837)	16.7 (14.2–19.3)	9.7 (7.8–11.9)	5.6 (4.2–7.4)	4.9 (3.5–6.6)
45–54 (n = 941)	15.4 (13.1–17.7)	9.8 (8.0–11.9)	5.7 (4.3–7.4)	4.8 (3.5–6.3)
55–65 (n = 753)	14.5 (12.0–17.0)	8.6 (6.7–10.9)	5.6 (4.1–7.5)	5.3 (3.8–7.2)

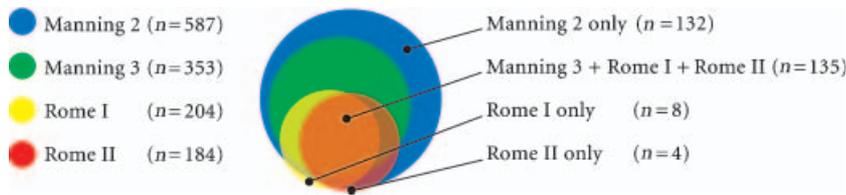


Figure 1. Overlap among IBS criteria

Symptoms

The diarrhoea-predominant form of IBS was more common than the constipation predominant, regardless of criteria. Of IBS-positive respondents, diarrhoea predominance ranged from 41 to 57%. Prevalence of diarrhoea among the total sample was 14.3%. Constipation occurred in 15.1% of all respondents. Constipation-predominant IBS was commonest among those fulfilling Rome I criteria (26.5%), but in the Rome II group constipation prevalence did not differ from that of the total sample (Table 4).

Of subjects meeting Rome I or Rome II criteria, 44% reported severe or very severe abdominal pain, and the comparable proportion of those meeting Manning 2 or Manning 3 criteria was 27 and 30%. Daily activities among both Rome groups were also more frequently disturbed because of the abdominal symptoms (Figure 2a,b). These findings were significant at 95% CI.

Of the total sample, 602 subjects (17.2%, 95% CI: 15.9–18.5) suffered from depression according to the RBDI (depression score 5 or more). The prevalence of depression was 30.6% (95% CI: 26.9–34.3) in Manning 2 group, 35.1% (95% CI: 30.0–40.1) in Manning 3, 42.9% (95% CI: 35.9–49.8) in Rome I, and 39.3% (95% CI: 32.1–46.5) in Rome II group. Depression was most frequent among those meeting any IBS criteria, and significantly more common in the Rome I group than in the Manning 2 group. Among the 602 subjects experiencing depression, prevalence of IBS according to Rome II was 11.7% for both sexes.

Anxiety was also almost twice as common among subjects meeting any IBS criteria than among controls but with no significant differences among any IBS diagnostic criteria (Table 4).

Use of health care resources

As expected, a greater proportion of those suffering from IBS, regardless of criterion, had visited a doctor for abdominal complaints at least once during the previous

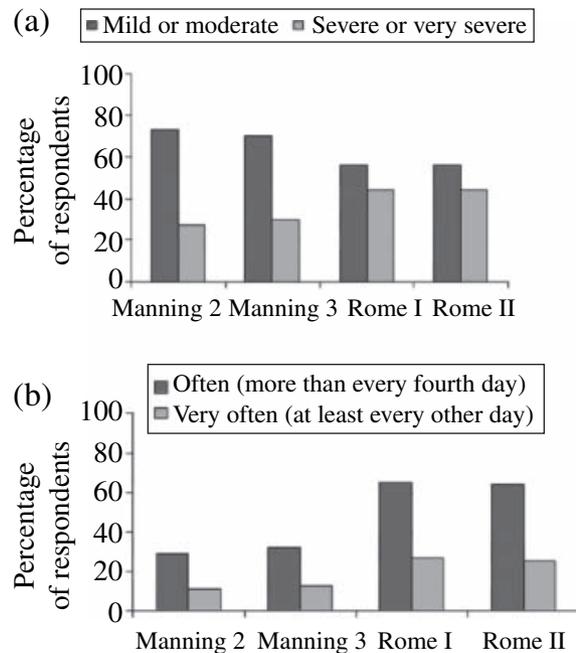


Figure 2. (a) Severity of abdominal pain; (b) daily activities disturbed by pain.

year than had controls. When we compared different IBS criteria we found that visiting a doctor was more common among Rome I and Rome II groups than among either Manning group (Figure 3). Visiting a doctor at least once for reasons other than abdominal complaints was also more frequent among subjects meeting any IBS criteria. No significant differences appeared between diagnostic criteria concerning this variable.

DISCUSSION

The Rome II Integrative Questionnaire, a new tool for epidemiological studies, was published in 2000, modified from an earlier version.¹⁷ To our knowledge, the literature at the moment offers no other studies applying the same instrument. Translation of the English questionnaire into Finnish may be a source of

Table 4. Sociodemographic and symptom characteristics of total sample and each IBS criterion

	Total (n = 3631)	Manning 2 (n = 587)	Manning 3 (n = 353)	Rome I (n = 204)	Rome II (n = 184)	P-value	P-value
Gender, n (%)							
Male	1639 (45.2)	209 (35.6)	132 (37.4)	81 (39.7)	80 (43.5)	P1 = 0.11	P1 = 0.64
Female	1991 (54.8)	378 (64.4)	221 (62.6)	123 (60.3)	104 (56.5)		
Mean age, years (s.d.)	42.3 (12.8)	41.4 (12.9)	41.5 (12.7)	42.5 (12.9)	42.2 (13.1)	P1 = 0.84	P1 = 0.89
Male	42.5 (12.8)	42.2 (12.6)	42.4 (12.3)	44.0 (12.3)	42.3 (12.5)	P2 = 0.18	P2 = 0.95
Female	42.1 (12.9)	41.0 (13.0)	41.0 (13.0)	41.5 (13.2)	42.1 (13.6)		
Marital status, n (%)							
Married or common law marriage	2411 (67.1)	398 (67.8)	248 (68.6)	138 (67.6)	120 (65.2)	P1 = 0.86	P1 = 0.31
Basic education, n (%)							
Common school or less	863 (24.1)	112 (19.2)	67 (19.1)	48 (23.6)	40 (22.0)	P1 = 0.02	P1 = 0.49
High school graduate	1182 (33.1)	192 (32.9)	119 (33.9)	55 (27.1)	50 (27.5)	P1 = 0.72	P1 = 0.10
Irregular working hours, n (%)	751 (21.2)	138 (24.0)	90 (26.1)	53 (26.6)	45 (25.1)	P1 = 0.02	P1 = 0.18
Depression, n (%)	602 (17.2)	175 (30.6)	120 (35.1)	84 (42.9)	70 (39.3)	P1**	P1**
Anxiety, n (%)	817 (22.7)	229 (39.4)	139 (39.6)	92 (45.3)	77 (42.1)	P1**	P1**
Diarrhoea, n (%)	521 (14.3)	242 (41.2)	168 (47.6)	110 (53.9)	104 (56.5)	P1**	P1**
Constipation, n (%)	548 (15.1)	133 (22.7)	66 (18.7)	54 (26.5)	30 (16.3)	P1**	P1 = 0.64
Visited physician at least once during previous year, n (%) because of							
Abdominal symptoms	538 (15.0)	187 (32.0)	117 (33.3)	100 (49.3)	88 (47.8)	P1**	P1**
Other reasons	2866 (79.7)	502 (85.7)	304 (86.3)	180 (88.7)	160 (87.0)	P1*	P1 = 0.012

P1 = P-value vs. those not meeting the criterion.

P2 = P-value male vs. female.

* p < 0.01; ** p < 0.0001.

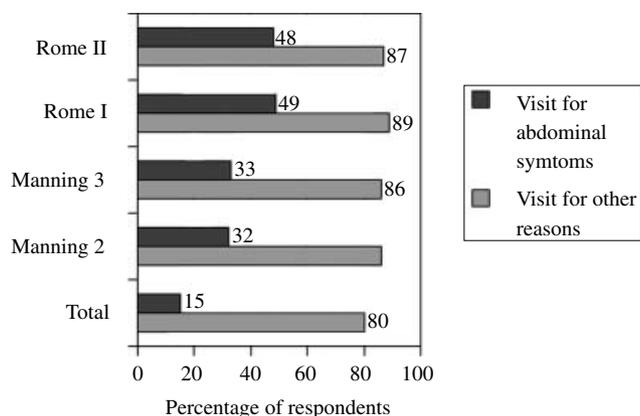


Figure 3. At least one visit to a physician during the previous year

bias as some expressions can have different meanings in different languages and cultures. However, back translation of the questionnaire into English did not reveal differences in the content of the items suggesting that translation into Finnish would not affect the number of IBS-positive subjects detected by the questionnaire. In our study, evaluation of a large random sample with a good overall response rate of 73% lends support to the reliability of the findings.

The prevalence of IBS, according to Manning 2, Manning 3, Rome I, and Rome II criteria shows substantial variation, depending on diagnostic criteria applied. In several epidemiological studies, IBS diagnosis has been based on fulfilment of two of the six Manning symptoms. In our study, this criterion will produce about threefold greater prevalence figures than will Rome II criteria, which has been recommended for use both in clinical studies and practice. This is in accordance with previously reported results from population-based studies.^{5, 6, 18} Almost all subjects who fulfil Rome II criteria will also fulfil Manning 2 criteria. Where to categorize those subjects having IBS according to Manning criteria but not according to Rome II? It is probable that some would fit into categories like 'functional constipation' or 'functional diarrhoea' where there is no requirement of pain. Rome criteria also include categories-like 'functional abdominal bloating' and 'unspecified functional bowel disorders', which would possibly apply to some of those patients that a clinician would diagnose as with IBS according to Manning criteria, but this issue needs to be studied further. In a recent study, Mearin *et al.*¹⁹ compared the original Rome⁸ to the Rome II criteria and found that only 31% of those meeting original Rome criteria met

Rome II criteria for IBS. Of those not meeting the new definition, 37% met the criteria for functional constipation, 7% for functional diarrhoea, 3% for functional abdominal bloating, and 1% for unspecified functional bowel disorder.

In our study, subjects fulfilling either of the Rome criteria had more severe abdominal symptoms than did those with two or three Manning symptoms. Of the six Manning symptoms, only three are associated with pain, while the others ('visible abdominal distension', 'passage of mucus', 'feeling of incomplete evacuation') are not pain-related, which may explain the differences in the severity of abdominal pain among Rome and Manning groups. In a previous study, those fulfilling Rome criteria have more severe abdominal symptoms and demonstrate higher levels of psychopathology such as depression, anxiety, and somatization than do those detected by Manning criteria, which is in accordance with our results.⁵ A larger proportion of our Rome-positive subjects had also consulted a doctor during the previous year for abdominal complaints. That a larger proportion of subjects who met any IBS criteria had also visited a doctor for reasons other than abdominal complaints may be due to an over-representation in IBS of depression and anxiety or possibly some other comorbidity.

The prevalence of depression and anxiety is higher among IBS sufferers than in the general population and depression seems even more frequent among those meeting either of the Rome criteria than those meeting Manning 2 criteria. Detection and adequate treatment of underlying depression may benefit the patient more than concentrating only on abdominal symptoms.

From the clinician's viewpoint, it is important to have diagnostic criteria applicable to clinical work. Rome II criteria seem reasonably handy for the clinician, because they are sufficiently short and simple to be useful in a busy practice. On the contrary, they leave the doctor the choice of how to ask the patient about symptom history. It may be possible to lead the interview in such a way that the doctor will obtain the required answers for the patient to fulfil Rome II criteria, although another clinician would disagree on such a diagnosis based on the same criteria. A clinician would probably base the diagnosis of IBS on a conversation with the patient and an impression of the patient's symptoms as a whole rather than on using a standardized questionnaire providing more standardized answers. Another important issue is the reliability

of the criteria for clinical work. The positive predictive value of Rome I criteria has been reported to be as high as 100% in a retrospective study,²⁰ but the specificity and sensitivity of Rome II criteria remains unknown.

New drugs are being developed for IBS, with the patients in the latest clinical drug trials selected based on Rome II criteria. It is important that clinicians be able to detect IBS by the same criteria, because the efficacy and safety of new drugs has been shown only in this patient population, which seems to differ from those fulfilling the older IBS definition. Otherwise, data from large drug studies is not readily applicable to all patients treated by general practitioners. On the contrary, it is possible that the indications for new IBS drugs will be broadened, for example, for functional constipation and functional diarrhoea, which could lessen this problem.

In conclusion, IBS is not as common an abdominal disorder by Rome II criteria as by Manning criteria. Rome II-positive IBS subjects seem to form a subgroup of Manning-positive subjects with higher levels of abdominal pain, more symptom-caused disturbance of daily activities, more mental symptoms, and more use of the health care system.

ACKNOWLEDGEMENTS

Authors thank Matti Siivola, MSc for statistical assistance. This research was supported by Mary and Georg C Ehrnrooth foundation, the Finnish foundation for gastroenterological research and Novartis Finland Oy.

REFERENCES

- 1 Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology* 1997; 112: 2120–37.
- 2 Delvaux M. Functional bowel disorders and irritable bowel syndrome in Europe. *Aliment Pharmacol Ther* 2003; 18(Suppl. 3): 75–9.
- 3 Manning AP, Thompson WG, Heaton KW, *et al.* Towards positive diagnosis of the irritable bowel. *Br Med J* 1978; 2: 653–4.
- 4 Kay L, Jorgensen T, Lannig C. Irritable bowel syndrome: which definitions are consistent? *J Int Med* 1998; 244: 489–94.
- 5 Boyce PM, Koloski NA, Talley NJ. Irritable bowel syndrome according to varying diagnostic criteria: are the new Rome II criteria unnecessarily restrictive for research and practise? *Am J Gastroenterol* 2000; 95: 3176–83.
- 6 Mearin F, Badia X, Balboa A, *et al.* Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. *Scand J Gastroenterol* 2001; 11: 1155–61.
- 7 Heaton KW, O'Donell LJD, Braddon FEM, *et al.* Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. *Gastroenterology* 1992; 102: 1962–7.
- 8 Thompson WG, Doteval G, Drossman DA, *et al.* Irritable bowel syndrome: guidelines for the diagnosis. *Gastroenterol Int* 1989; 2: 92–5.
- 9 Thompson WG, Creed F, Drossman DA, *et al.* Functional bowel disease and functional abdominal pain. *Gastroenterol Int* 1992; 5: 75–91.
- 10 Thompson WG, Longstreth GF, Drossman DA, *et al.* Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45: 43–7.
- 11 Drossman DA, Corazziari E, Talley NJ, *et al.* (eds). *The functional gastrointestinal disorders*. 2nd edn. McLean, VA, USA: Degnon Associates, 2000 (Appendix C): 690–714.
- 12 Beck AT, Beck RW. Screening depressed patients in family practise. *Postgrad Med* 1972; 52: 81–5.
- 13 Beck A, Rial W, Rickels K. Short form of depression inventory: crossvalidation. *Psychol Rep* 1974; 34: 1184–6.
- 14 Raitasalo R, Notkola V. Screening of mental health disorders among farmers and occupational health care. *J Soc Med* 1987; 24: 232–41.
- 15 Hänninen V, Aro H. Sex differences in coping and depression among young adults. *Soc Sci Med* 1996; 43: 1453–60.
- 16 Fleiss JL. *Statistical Methods for Rates and Proportions*, 2nd edn. New York: John Wiley and Sons, 1981.
- 17 Drossman DA, Richter JE, Talley NJ, *et al.* *The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment*. McLean, VA: Degnon Associates, 1994: 339–45.
- 18 Hungin APS, Whorwell PJ, Tack J, *et al.* The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40 000 subjects. *Aliment Pharmacol Ther* 2003; 17: 643–50.
- 19 Mearin F, Roset M, Badia X, *et al.* Splitting irritable bowel syndrome: from original Rome to Rome II criteria. *Am J Gastroenterol* 2004; 99: 122–30.
- 20 Vanner SJ, Depew WT, Paterson WG, *et al.* Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* 1999; 94: 2912–17.