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Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia

Background and study aims: Upper gastrointestinal endoscopy in patients with functional dyspepsia is often carried out merely to reassure patients that symptoms are not due to serious pathology. The aim of this study was to compare anxiety, depression, and health-related quality of life as proxy values for reassurance in patients with functional dyspepsia before and after upper gastrointestinal endoscopy.

Patients and methods: Consecutive patients referred for endoscopy between February 2002 and February 2004 were included in the study. They were asked to score anxiety and depression using the Hospital Anxiety and Depression Scale, health-related quality of life using the EuroQol-5D questionnaire, and their impression of their own general health using a visual analogue scale, 2 weeks before endoscopy and again 1 month afterwards.

Results: A total of 420 patients were included, 42% of whom were found to have an organic abnormality of some sort during upper gastrointestinal endoscopy. Neither the anxiety nor the depression frequencies differed significantly before and after endoscopy, either in patients with organic abnormalities at endoscopy or in those without. The general impression of health did not change after endoscopy either: organic abnormalities 62.7 ± 27.4 vs. 64.9 ± 24.2, $P = 0.28$; functional dyspepsia 61.0 ± 27.9 vs. 62.8 ± 27.2, $P = 0.39$. Only patients who had organic abnormalities reported a slightly improved quality of life 1 month after endoscopy: 0.74 ± 0.15 vs. 0.78 ± 0.12, $P < 0.01$.

Conclusion: In patients with functional dyspepsia, upper gastrointestinal endoscopy does not improve psychological well-being or health-related quality of life. In view of the invasiveness, cost, and potential harm associated with endoscopy, careful consideration should be given to whether this procedure should be carried out merely for the sake of the patient's "peace of mind".

Introduction

Functional dyspepsia – defined as the presence of persistent upper gastrointestinal symptoms without evidence of an organic disease that is likely to explain the symptoms – continues to be an important clinical problem. In general, treatment is aimed at inhibiting gastric acid, but in most patients this is insufficient and symptoms persist [1–3]. In these patients, upper gastrointestinal endoscopy is often carried out in order to exclude serious pathology in the proximal gut, thereby providing reassurance to the physician and, in particular, to the patient [4].

Extensive research has been conducted on the psychological aspects of functional gastrointestinal diseases. In a study by Quadri and Vakil, it was shown that health-related anxiety declines after open-access endoscopy in patients who have high to moderate anxiety at the baseline [5]. Other studies have found that patients with functional dyspepsia are more anxious and depressed

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Bibliography
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in comparison with healthy control individuals or patients in whom the symptoms have an organic cause [6–11], and that the health-related quality of life (HRQL) is impaired in patients with functional dyspepsia in comparison with healthy control individuals and patients with other chronic disorders such as asthma [12–15].

By contrast, we demonstrated in a recent study that there is no difference in the level of anxiety or depression between patients with and without an organic cause of their symptoms before gastrointestinal endoscopy [16]. Attempts have been made to quantify the effect of a negative endoscopy on HRQL [17], and a few studies have concluded that psychological well-being and HRQL improve along with the improvement of symptoms [12,18]. On the basis of these results, it was concluded that psychological distress develops as a result of the disorder, rather than causing the symptoms itself. Taking this into account, the policy of carrying out upper gastrointestinal endoscopy in order to reassure the patient appears illogical, since the diagnostic procedure is not likely to resolve the symptoms and will therefore not contribute to the patient's psychological well-being.

The objective of the present study was to investigate whether there are any differences in the level of psychological distress and in the HRQL, as proxy values for reassurance, before and after upper gastrointestinal endoscopy, between patients with and without an organic abnormality underlying the symptoms.

Patients and methods

Patients

Between February 2002 and February 2004, consecutive patients referred for the first time for upper gastrointestinal endoscopy to the Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands, were included. The institution is a general secondary-care district hospital. All of the patients were referred in accordance with the relevant guidelines in the Netherlands for general practitioners regarding the management of patients with dyspepsia. The guidelines state that an endoscopy is indicated if alarm symptoms are present, when the general practitioner needs reassurance that there is no serious pathology underlying the symptoms, or if symptoms recur or persist after empirical treatment with a proton-pump inhibitor (PPI) and *Helicobacter pylori* eradication treatment.

It was not feasible to exclude in advance any patients who had already undergone endoscopy during the previous 6 months. All patients referred for upper gastrointestinal endoscopy were therefore sent a questionnaire 2 weeks in advance of their appointments. The patients were informed that they should return the questionnaire only if they had not had a previous upper gastrointestinal endoscopy in the previous 6 months. The questionnaire included enquiries regarding demographic data, the presence and severity of gastrointestinal symptoms, anxiety and depression, and health-related quality of life (HRQL). The questionnaire was repeated 1 month after the endoscopy, except for the questions concerning demographic data. All of the questionnaires were processed using the Teleform automatic scanning program, version 6.0 (Cardiff Software, Inc., Sunnyvale, California, USA). All aspects of the protocol were approved by the medical ethics committees of Radboud University Nijmegen Medical Center and the Canisius-Wilhelmina Hospital, both in Nijmegen in the Netherlands.

Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). This is a self-completed questionnaire that has been validated and can be used in a variety of clinical settings [19–21]. It consists of 14 items and is divided into an anxiety subscale and a depression subscale, each consisting of seven questions rated on a scale ranging from 0 to 3, depending on the severity of the problem described in the question. This allows utilities to be calculated that indicate the individual's degree of anxiety or depression. A subscale score below 8 is considered normal – i.e., showing no signs of anxiety or depression [22]. Patients were defined as having mild to severe anxiety or depression if they scored 8 or more on one of the respective subscales, although clinical signs might have been absent. Questions that were not filled out properly were not used for further analysis.

Health-related quality of life

The patients' HRQL was assessed using the EuroQol-5D (EQ-5D) questionnaire, and their general impression of their own health in the previous weeks was assessed using a 100-mm visual analogue scale (VAS). The EQ-5D is a widely used multiple-attribute system suitable for assessing states of health. The EQ-5D classification describes health status in relation to five domains: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression at three levels, with 1 representing no dysfunction at all and 3 representing severe dysfunction. The validity and reliability of the questionnaire have been tested in a wide range of patient groups [23,24]. The VAS is a line with a standard length, with the extremes of the responses at each end. The scale ranges from 0 to 100, with 0 being the worst imaginable HRQL and 100 being the best. The patient is asked to mark the line at an appropriate point, and the score is then obtained by measuring the distance from the beginning of the line to that point.

Symptom score

Patients were asked to complete a questionnaire including 32 items concerning gastrointestinal symptoms. The severity of the symptoms during the previous 4 weeks was rated on a 7-point Likert scale (with 0 meaning "absent" and 6 "very severe"). A score of two or more was regarded as symptom presence.

Endoscopy

The patients underwent routine diagnostic upper gastrointestinal endoscopy, and the outcomes were entered into a database. If necessary, histological data were obtained from biopsies taken during the endoscopy. The biopsies were analyzed by an experienced pathologist, and the results were entered into the same database. The results were retrieved from the database, and patients were divided into groups according to their most prominent endoscopic outcome: carcinoma, gastric or duodenal ulcer, reflux esophagitis, other (e.g., esophageal varices, hiatal hernia, or fungus), and no organic abnormality underlying the symptoms. When no endoscopic or histological explanation for the symptoms was found, the patients were defined as having functional dyspepsia.

Table **1** Demographic data for the study group (n = 420)

	Functional dyspepsia (n = 245)		*Organic abnormalities (n = 175)*		
	n	*%*	*n*	*%*	P
Male	104	42	93	53	< 0.05
Previous endoscopy [1]	89	36	73	42	0.26
Current smoking	34	14	31	18	0.28
Alcohol use [2]	49	20	55	31	< 0.05
Coffee consumption [3]	101	41	77	44	0.57
Dutch nationality	219	90	162	94	0.16
Mean age (± SD)	53 ± 15		57 ± 14		0.01

[1] Either upper gastrointestinal endoscopy, lower gastrointestinal endoscopy, or sigmoidoscopy.
[2] The median consumption was 7 units/week. The numbers shown are for patients consuming more than 7 units/week.
[3] The median consumption was 20 units/week. The percentages shown are for patients consuming more than 20 units/week.

Afterwards, the patients were informed of the outcome of the endoscopy. If there was an organic abnormality, appropriate treatment was started; when there was no organic abnormality, the patients were reassured that there was no severe pathology underlying their symptoms.

Statistical analyses

Statistical analysis was carried out using the SAS statistics program, version 8.0 (SAS Institute, Inc., Minneapolis, Minnesota, USA). Data at baseline were analyzed using frequency tables and descriptive statistics. Patients with incomplete data were excluded from further analysis. A paired *t* test was used to assess within-subject differences in the mean scores for anxiety, depression, HRQL, and the number of symptoms before and after endoscopy. The difference in the severity of symptoms was assessed using Wilcoxon's signed-rank test. The influence of other variables on differences before and after endoscopy was assessed using linear regression models. Pearson's chi-squared test was used to assess differences in the variables listed in Table **1**. Patients with coffee and alcohol consumption were divided into two groups depending on the median number of units consumed per week (20 and 7, respectively). A *P* value of < 0.05 was considered statistically significant. Correlations between the total HADS scores, symptom severity, and the number of symptoms were calculated using Spearman's rank correlation.

Results

A total of 1769 questionnaires were sent and 932 were returned, 280 of which had to be excluded, as investigation of medical records showed that the patients had undergone an upper gastrointestinal endoscopy during the previous 6 months. The remaining 652 patients received the same questionnaire 1 month after endoscopy, and 515 of these questionnaires were returned. Ninety-five responders had to be excluded due to incomplete questionnaires. Complete responses were available for 420 of the initial 652 patients (64.4%; 197 men, 223 women; mean age 55 ± 15 years).

A total of 175 patients were found to have an organic abnormality at endoscopy: 2% had carcinoma, 7% had gastric ulcers, 5% had duodenal ulcers, 55% had reflux esophagitis, and 31% had another disorder (e.g., fungus, hiatal hernia). The patients with organic abnormalities were statistically significantly older, more often male, and consumed more alcohol in comparison with patients without an organic abnormality (Table **1**). A previous diagnostic intervention for upper gastrointestinal symptoms, other than endoscopy (i.e., radiography, *H. pylori* testing), was reported by 39% of the overall group of patients, and the previous interventions were equally distributed among patients with and without an organic disorder at endoscopy (organic disorder vs. functional dyspepsia: 37% vs. 31% for radiography, *P* = 0.19 and 12% vs. 11% for *H. pylori*, *P* = 0.76). Patients who reported having undergone a previous endoscopy (> 6 months before the index endoscopy) were neither more anxious nor more depressed at baseline than patients who did not (OR 1.0; 95% CI, 0.6 – 1.5; and OR 1.3; 95% CI, 0.8 – 2.0, respectively). None of the variables listed in Table **1** were associated with a higher risk of anxiety, depression, or reduced HRQL.

When the mean scores on the Hospital Anxiety and Depression Scale (HADS) before and after endoscopy were compared, only patients with an organic abnormality at endoscopy were found to show an improvement in anxiety scores (Table **2**). Using the cut-off point of a score of 8 or more per subscale, 31% of the patients with an organic abnormality were anxious at baseline, in comparison with 28% after endoscopy (*P* = 0.56), while 35% of the patients with functional dyspepsia were anxious at baseline in comparison with 31% after endoscopy (*P* = 0.33). Depression was present in 27% of the patients in both groups, both before and after endoscopy.

The general impression of health measured with the visual analogue scale did not improve over time in either group, nor were there any differences between the two groups before and after endoscopy. Patients with an organic abnormality at endoscopy reported a slight increase in the HRQL after endoscopy: mean 0.74 ± 0.15 at T0 vs. 0.78 ± 0.12 at T1 (*P* < 0.01). Both groups of patients, with and without an organic abnormality, reported a statistically significant improvement in symptom severity scores and a reduction in the mean number of symptoms (Table **2**). Linear regression analysis showed that none of the differences found in the outcomes listed in Table **2** were influenced by sex, age, alcohol consumption, or the presence of an organic disorder (Table **3**).

Table **2** Anxiety, depression, impression of general health, and quality of life before (T0) and after (T1) upper gastrointestinal endoscopy: subdivision in organic and functional dyspepsia

	n	*T0* *Mean ± SD*	*T1* *Mean ± SD*	*Mean difference (95% CI)*	P
Anxiety					
Organic abnormalities	169	5.8 ± 3.8	5.3 ± 4.0	0.57 (0.15 to 0.99)	< 0.01
Functional dyspepsia	228	6.3 ± 4.4	6.2 ± 4.4	0.21 (–0.18 to 0.61)	0.28
Depression					
Organic abnormalities	169	5.1 ± 3.7	4.9 ± 4.1	0.21 (–0.17 to 0.60)	0.28
Functional dyspepsia	236	5.3 ± 4.3	5.3 ± 4.5	– 0.03 (–0.40 to 0.34)	0.87
VAS					
Organic abnormalities	175	62.7 ± 27.4	64.9 ± 24.2	– 2.16 (–6.06 to 1.74)	0.28
Functional dyspepsia	245	61.0 ± 27.9	62.8 ± 27.2	– 1.73 (–5.70 to 2.22)	0.39
HRQL					
Organic abnormalities	177	0.74 ± 0.15	0.78 ± 0.12	– 0.04 (–0.05 to –0.02)	< 0.01
Functional dyspepsia	236	0.72 ± 0.17	0.72 ± 0.18	0.00 (–0.02 to 0.02)	0.80
Number of symptoms					
Organic abnormalities	175	9.4 ± 6.2	8.0 ± 6.4	1.33 (0.72 to 1.93)	< 0.01
Functional dyspepsia	244	9.7 ± 6.5	8.8 ± 6.8	0.86 (0.30 to 1.42)	< 0.01
Severity of symptoms					
Organic abnormalities	175	68.9 ± 52.7	57.2 ± 49.6	11.64 (3.79 to 19.49)	< 0.01
Functional dyspepsia	244	76.5 ± 63.1	60.7 ± 53.1	15.77 (7.87 to 23.66)	< 0.01

T0, 2 weeks before endoscopy; T1, 1 month after endoscopy; VAS, visual analogue scale measuring health-related quality of life in the previous week; HRQL, health-related quality of life.

Table **3** Multivariate linear regression analysis of the influence of various variables on the differences of outcome variables between T0 and T1

	Anxiety		*Depression*		*VAS*		*HRQL*		*No. of symptoms*		*Symptom severity*	
	β	R^2	β	R^2	β	R^2	β	R^2	β	R^2	β	R^2
Organic abnormality	0.35	0.00	0.24	0.00	1.39	0.00	– 0.04	0.02	0.46	0.00	– 4.13	0.00
Sex	0.04	0.00	– 0.28	0.00	– 0.35	0.00	0.00	0.00	– 0.01	0.00	– 9.50	0.01
Age	– 0.02	0.02	– 0.02	0.01	– 0.11	0.01	0.00	0.00	– 0.01	0.00	0.07	0.00
Alcohol usage	0.50	0.00	0.60	0.01	2.37	0.01	– 0.04	0.02	– 0.14	0.00	7.05	0.00
Complete model		0.03		0.03		0.02		0.04		0.01		0.01

β, regression coefficient, representing the amount the dependent variable variable changes when the corresponding independent changes by one unit; R^2, the total variance in the model explained by a specific variable. T0, 2 weeks before endoscopy; T1, 1 month after endoscopy; VAS, visual analogue scale measuring health-related quality of life in the past week; HRQL, health-related quality of life.

Finally, an increase in the total number of symptoms (Figure **1**) was associated with an increase in mean scores on the HADS (correlation coefficient $r = 0.78$; $P < 0.05$). Figure **2** shows that when the total numbers of reported symptoms were divided into subgroups, the proportion of patients reporting mild to severe anxiety and depression also increased with an increasing number of symptoms. However, an increase in the severity of symptoms (Figure **3**) was not associated with an increase in the mean total anxiety and depression scores ($r = 0.17$, $P < 0.05$).

Discussion

Functional dyspepsia has often been associated with psychological distress [9]. This study, including a large sample, investigated whether endoscopy improves psychological well-being in these patients. Although a reduction in the severity of the symptoms was observed, patients with functional dyspepsia did not appear to benefit from endoscopy. This finding is noteworthy, since it has often been stated that the main reason for carrying out an endoscopic examination is to provide the patient with reassurance [25,26].

Although patients who were found to have an organic abnormality at endoscopy reported a statistically significant improvement in their health-related quality of life (HRQL), the difference was so small (0.04 on a scale ranging from 0 to 1) that it has little or no clinical relevance. The improvement in symptom severity and in the mean number of symptoms in these patients was also statistically significant, probably due to the treatment received after endoscopy. Nevertheless, when the mean improvement in the number of symptoms is compared between patients with an organic abnormality and patients with functional dyspepsia, the difference in the improvement is only 0.5 symptoms. In addition, both groups of patients still had a considerable number of symptoms after endoscopy, with an average of 8 or more.

Using anxiety, depression, and HRQL as proxy measures for reassurance, it was found that endoscopy does not reassure patients with upper abdominal symptoms. These results are in accord-

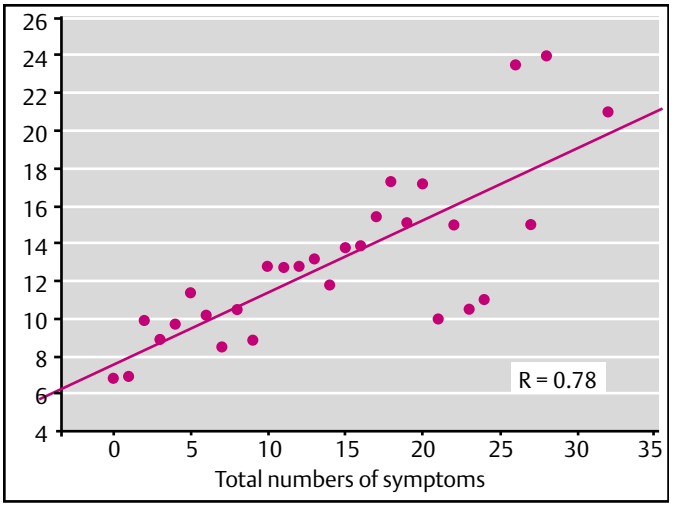

Figure **1** Correlation between the total number of symptoms during the previous 4 weeks and the mean scores on the Hospital Anxiety and Depression Scale (HADS).

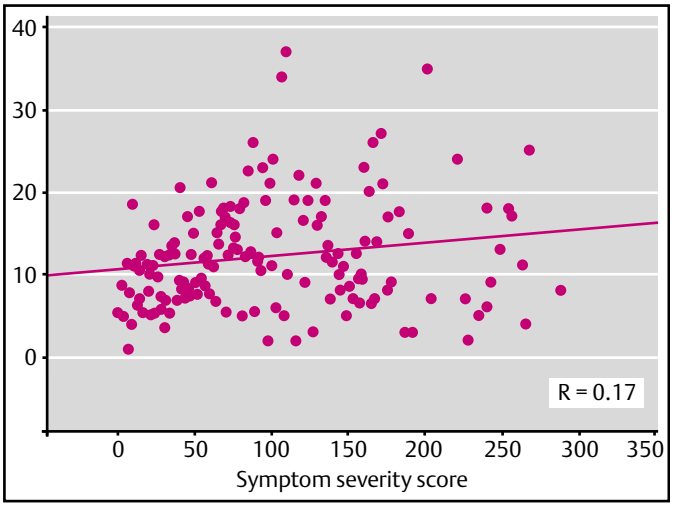

Figure **3** Correlation between the symptom severity during the previous 4 weeks and the total score on the Hospital Anxiety and Depression Scale (HADS).

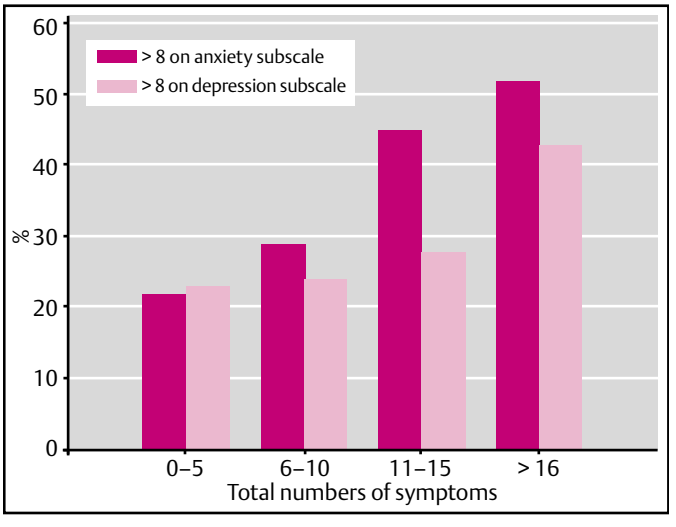

Figure **2** The proportion of patients reporting mild to severe anxiety and depression on the Hospital Anxiety and Depression Scale.

were originally recruited for a double-blind, randomized clinical study to compare omeprazole with a placebo [26]. Patients' belief that they were ill and their worry about health were measured 1 week before and immediately before endoscopy and immediately, 24 h, 1 week, 1 month, and 1 year after endoscopy, with patients being reassured that "there is nothing seriously wrong". The results showed that immediately after the endoscopy, both the patients' belief that they were ill and their worry about health decreased, but that the values returned to normal during the follow-up. In combination with the present results, this suggests that the initial improvement is only of brief duration and disappears a month after endoscopy. The studies by both Wiklund et al. [25] and Lucock et al. [26] involve some major limitations in the study design that may have distorted the results. In addition, the time between the measurements was very short, so that the results may have been influenced by recognition bias. This casts doubt on the reported initial improvement in psychological well-being, which probably did not exist at all.

ance with those reported recently by Spiegel et al. [27], who investigated the effect of endoscopy in patients with another functional gastrointestinal disorder, irritable bowel syndrome, and found no independent association between a negative colonoscopy and reassurance or an improved HRQL in these patients.

Several other studies have investigated the role of endoscopy in patients with dyspepsia. In the past, it has been concluded that endoscopy is a cost-effective strategy in the management of patients presenting with dyspepsia [28]. More recent studies have shown that "test-and-treat" *H. pylori* and/or empirical PPI treatment are as safe and effective, or even more effective, than prompt endoscopy [29–32]. The effect of an endoscopic examination on psychological well-being was also investigated by Wiklund et al. [25]. They measured psychological well-being and HRQL 1 week before and 1 week after endoscopy and found that endoscopy itself led to an improvement in both measures [25]. Comparable results were found in a study in the USA including 60 patients with no organic cause for symptoms, who Quadri and Vakil reported an improvement of six points on a scale ranging from 0 to 84 in health-related anxiety among patients with high and moderate anxiety scores before endoscopy [5]. They used a disease-specific measure capable of detecting small alterations in health-related anxiety to assess the effect of open-access endoscopy. Although they reported a statistically significantly improvement, the clinical relevance of a 7% improvement on a disease-specific scale is debatable. The present study was designed to assess clinically relevant changes in psychological well-being. It is often stated that generic measures are limited because of their limited ability to detect small differences. We used generic measures to assess generally experienced anxiety, depression, and HRQL and combined these data with a symptom questionnaire. In this study, this does not constitute a problem, and in fact a generic measure is preferable due to the advantage of generalizability to other populations [33].

No correlation was found between the severity of symptoms and the mean total HADS scores. This is in accordance with results

In brief

It has always been considered that a negative endoscopic examination in a symptomatic patient (especially in those with dyspepsia) has a positive effect in providing the patient with reassurance. This study argues against this assumption on the basis of patients' Hospital Anxiety and Depression Scale scores before and after endoscopy. Neither these parameters nor the quality-of-life score changed in patients who had no organic abnormalities. In patients who did have organic abnormalities, at least the quality of life improved slightly.

described by Jones et al. [34] in a study including 151 consecutive patients with functional dyspepsia and 90 healthy individuals, who scored their psychological distress and symptoms on validated questionnaires. We would endorse the authors' conclusion that these correlations are too weak for it to be concluded that there is a relation between the severity of symptoms and psychological distress.

The response rate to the first questionnaire was quite low. This was due to the fact that all of the patients referred for upper gastrointestinal endoscopy received a questionnaire. Many patients may have considered themselves ineligible for participation in the trial because they had undergone an upper gastrointestinal endoscopy during the previous 6 months, or had an inadequate command of the Dutch language used in the questionnaire. These assumptions were confirmed by a random check on the medical records of over 10% of the nonresponders. The actual response rate for patients undergoing their first upper gastrointestinal endoscopy was 64.4%, and a response bias can therefore not be completely excluded. It is conceivable that patients with a psychiatric disorder might be either more likely or unlikely than others to return the questionnaire. However, in general, the groups of patients with and without an organic abnormality had equal scores for anxiety and depression, HRQL, and symptom severity. There is therefore no reason to assume that the response rates were different between the two groups. If any response bias is present, we would assume that it is equally distributed across both groups.

In summary, although there appears to be an improvement in symptom severity after endoscopy, there is no clinically relevant improvement in the psychological well-being and HRQL of patients with upper gastrointestinal symptoms. In view of the invasiveness, cost, and potential harm associated with upper gastrointestinal endoscopy, very careful consideration should be given to whether this procedure should be carried out merely for the sake of the patient's "peace of mind".

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Competing interests: None

References

[1] Peura DA, Kovacs TO, Metz DC et al. Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. Am J Med 2004; 116: 740 – 748
[2] Talley NJ, Meineche-Schmidt V, Pare P et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther 1998; 12: 1055 – 1065
[3] Wong WM, Wong BC, Hung WK et al. Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients. Gut 2002; 51: 502 – 506
[4] Stanghellini V, Tosetti C, Barbara G et al. Review article: the continuing dilemma of dyspepsia. Aliment Pharmacol Ther 2000; 14 (Suppl 3): 23 – 30
[5] Quadri A, Vakil N. Health-related anxiety and the effect of open-access endoscopy in US patients with dyspepsia. Aliment Pharmacol Ther 2003; 17: 835 – 840
[6] Drossman DA, Talley NJ, Leserman J et al. Sexual and physical abuse and gastrointestinal illness: review and recommendations. Ann Intern Med 1995; 123: 782 – 794
[7] Drossman DA, Creed FH, Olden KW et al. Psychosocial aspects of the functional gastrointestinal disorders. Gut 1999; 45 (Suppl 2): II25 – II30
[8] Koloski NA, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol 2002; 97: 2290 – 2299
[9] Locke GR 3rd, Weaver AL, Melton LJ 3rd, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. Am J Gastroenterol 2004; 99: 350 – 357
[10] Whitehead WE, Bosmajian L, Zonderman AB et al. Symptoms of psychologic distress associated with irritable bowel syndrome: comparison of community and medical clinic samples. Gastroenterology 1988; 95: 709 – 714
[11] Haug TT, Svebak S, Wilhelmsen I et al. Psychological factors and somatic symptoms in functional dyspepsia: a comparison with duodenal ulcer and healthy controls. J Psychosom Res 1994; 38: 281 – 291
[12] Mones J, Adan A, Segu JL et al. Quality of life in functional dyspepsia. Dig Dis Sci 2002; 47: 20 – 26
[13] Chang L. Review article: epidemiology and quality of life in functional gastrointestinal disorders. Aliment Pharmacol Ther 2004; 20 (Suppl 7): 31 – 39
[14] El-Serag HB, Talley NJ. Health-related quality of life in functional dyspepsia. Aliment Pharmacol Ther 2003; 18: 387 – 393
[15] Bovenschen HJ, Laheij RJ, Tan AC et al. Health-related quality of life of patients with gastrointestinal symptoms. Aliment Pharmacol Ther 2004; 20: 311 – 319
[16] van Kerkhoven LA, van Rossum LG, van Oijen MG et al. Anxiety, depression and psychotropic medication use in patients with persistent upper and lower gastrointestinal symptoms. Aliment Pharmacol Ther 2005; 21: 1001 – 1006
[17] Sonnenberg A, Vakil N. The benefit of negative tests in non-ulcer dyspepsia. Med Decis Making 2002; 22: 199 – 207
[18] Wilhelmsen I, Berstad A. Reduced relapse rate in duodenal ulcer disease leads to normalization of psychological distress: twelve-year follow-up. Scand J Gastroenterol 2004; 39: 717 – 721
[19] Herrmann C. International experiences with the Hospital Anxiety and Depression Scale: a review of validation data and clinical results. J Psychosom Res 1997; 42: 17 – 41
[20] Spinhoven P, Ormel J, Sloekers PP et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997; 27: 363 – 370
[21] Johnston M, Pollard B, Hennessey P. Construct validation of the hospital anxiety and depression scale with clinical populations. J Psychosom Res 2000; 48: 579 – 584
[22] Crawford JR, Henry JD, Crombie C et al. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 2001; 40: 429 – 434
[23] Greiner W, Weijnen T, Nieuwenhuizen M et al. A single European currency for EQ-5D health states: results from a six-country study. Eur J Health Econ 2003; 4: 222 – 231

[24] van Agt HM, Essink-Bot ML, Krabbe PF et al. Test–retest reliability of health state valuations collected with the EuroQol questionnaire. Soc Sci Med 1994; 39: 1537 – 1544
[25] Wiklund I, Glise H, Jerndal P et al. Does endoscopy have a positive impact on quality of life in dyspepsia? Gastrointest Endosc 1998; 47: 449 – 454
[26] Lucock MP, Morley S, White C et al. Responses of consecutive patients to reassurance after gastroscopy: results of self administered questionnaire survey. BMJ 1997; 315: 572 – 575
[27] Spiegel BM, Gralnek IM, Bolus R et al. Is a negative colonoscopy associated with reassurance or improved health-related quality of life in irritable bowel syndrome? Gastrointest Endosc 2005; 62: 892 – 899
[28] Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H_2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994; 343: 811 – 816
[29] Ford AC, Qume M, Moayyedi P et al. *Helicobacter pylori* "test and treat" or endoscopy for managing dyspepsia: an individual patient data meta-analysis. Gastroenterology 2005; 128: 1838 – 1844
[30] Laheij RJ, Hermsen JT, Jansen JB et al. Empirical treatment followed by a test-and-treat strategy is more cost-effective in comparison with prompt endoscopy or radiography in patients with dyspeptic symptoms: a randomized trial in a primary care setting. Fam Pract 2004; 21: 238 – 243
[31] Laheij RJ, van Rossum LG, Heinen N et al. Long-term follow-up of empirical treatment or prompt endoscopy for patients with persistent dyspeptic symptoms? Eur J Gastroenterol Hepatol 2004; 16: 785 – 789
[32] Lassen AT, Hallas J, Schaffalitzky de Muckadell OB. *Helicobacter pylori* test and eradicate versus prompt endoscopy for management of dyspeptic patients: 6.7 year follow up of a randomised trial. Gut 2004; 53: 1758 – 1763
[33] Bovenschen HJ, Rossum LG, Oijen MGH et al. Health-related quality of life as an outcome in research. Drug Benefit Trends 2004; 16: 544 – 556
[34] Jones MP, Sharp LK, Crowell MD. Psychosocial correlates of symptoms in functional dyspepsia. Clin Gastroenterol Hepatol 2005; 3: 521 – 528