Is it possible to clinically differentiate erosive from nonerosive reflux disease patients? A study using an artificial neural networks-assisted algorithm

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Background **The use of either symptom questionnaires or artificial neural networks (ANNs) has proven to improve the accuracy in diagnosing gastroesophageal reflux disease (GERD). However, the differentiation between the erosive and nonerosive reflux disease based upon symptoms at presentation still remains inconclusive.**

Aim **To assess the capability of a combined approach, that is, the use of a novel GERD questionnaire – the QUestionario Italiano Diagnostico (QUID) questionnaire – and of an ANNs-assisted algorithm, to discriminate between nonerosive gastroesophageal reflux disease (NERD) and erosive esophagitis (EE) patients.**

Methods **Five hundred and fifty-seven adult outpatients with typical GERD symptoms and 94 asymptomatic adult patients, were submitted to the QUID questionnaire. GERD patients were then submitted to upper gastrointestinal endoscopy to differentiate them between EE and NERD patients.**

Results **The QUID score resulted significantly ($P<0.001$) higher in GERD patients versus controls, but it was not statistically significantly different between EE and NERD patients. ANNs assisted diagnosis had greater specificity, sensitivity and accuracy compared with the linear discriminant analysis only to differentiate GERD patients from controls. However, no single technique was able to satisfactorily discriminate between EE and NERD patients.**

Conclusion **Our study suggests that the combination between QUID questionnaire and an ANNs-assisted algorithm is useful only to differentiate GERD patients from healthy individuals but fails to further discriminate erosive from nonerosive patients.** ***Eur J Gastroenterol Hepatol*** **22:1163–1168 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In 2005 we described a novel algorithm approach based on the use of artificial neural networks (ANNs) to achieve a diagnosis of gastroesophageal reflux disease solely on the basis of clinical data with a predictive accuracy of 85% [1]. In that study, we used a validated symptom questionnaire (the GERQ by Mayo Clinic) [2] and upper gastrointestinal (GI) endoscopy and pH-metry to identify erosive esophagitis (EE) patients or pathological refluxers, respectively. Furthermore, we were able to build up a new symptom questionnaire, called 'QUestionario Italiano Diagnostico' (QUID) which was constructed by application of ANNs which selected those items from GERQ found to be mostly correlated with the diagnosis of gastroesophageal reflux disease (GERD).

In the present multicenter collaborative study, we prospectively tested a large population (577 individuals) of GERD patients (with and without EE) and 94 healthy individuals to further assess the diagnostic validity of the QUID questionnaire combined with the use of ANNs to differentiate GERD versus control individuals and, within the GERD population, nonerosive gastroesophageal reflux (NERD) versus EE patients. The performance of various kinds of ANNs in these discriminations was compared with that of traditional linear discriminant analysis (LDA).

Methods

The study was conducted between June 2003 and June 2005 according to Good Clinical Practices. All ethics committees of the participating centres granted authorization and written informed consent was obtained from all patients.

Five hundred and seventy-seven adult outpatients (282 females and 295 males, average age 43.5 ± 12.4 years), with typical GERD symptoms, referred to the various

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Table 1 Demographic features of study population

	EE patients 306/577 (53%)	NERD patients 271/577 (47%)	Healthy volunteers 94
Male	194 (63.4%)	101 (37.3%)	74 (78.7%)
Female	112 (36.6%)	170 (62.7%)	20 (21.3%)
Age (years), mean ± SD	43.6 ± 12.22	43.42 ± 12.56	45.09 ± 6.90
Height (cm), mean (± SD)	169.86 (± 8.63)	166.84 (± 8.14)	173.31 (± 8.47)
Weight (kg), mean (± SD)	75.33 (± 15.40)	68.49 (± 12.41)	74.98 (± 12.72)
Smoking, no	164 (53.6%)	115 (42.4%)	42 (44.7%)

EE, erosive esophagitis; NERD, nonerosive reflux disease.

centres to undergo a diagnostic upper GI endoscopy, were recruited by 60 gastroenterological Italian centres and were submitted to the QUID questionnaire for a complete symptom assessment. The 94 control healthy individuals were chosen among otherwise healthy workers aged more than 18 and less than 60 years without any symptom of GERD.

The demographic data of the patient sample and of healthy individuals according to the endoscopic findings (EE vs. NERD patients) are shown in Table 1.

Inclusion criteria

Patients were included provided that, before endoscopic examination, the following criteria were fulfilled:

(1) Age between 18 and 65.
(2) Presence of heartburn symptoms for at least 15 days, at least once a day.
(3) Referral by treating physician to undergo upper GI endoscopy.
(4) Ability to read and write Italian, more than 5 years of schooling.
(5) Consent to voluntary participation with signature on the Informed Consent form before study screening.

Exclusion criteria

Patients who had one or more of these criteria at baseline were excluded from the study:

(1) Treatment with proton pump inhibitors (PPI) in the month preceding endoscopy.
(2) Diagnosis of esophagitis established during the past 12 months.
(3) Pregnancy and/or lactation.
(4) Concomitant clinically severe diseases during the 4 weeks preceding the study, requiring any pharmacological treatment.

QUID questionnaire

QUID is a 41-item questionnaire which investigates frequency and intensity of many esophageal and extra-esophageal GERD symptoms of and a number of social and demographic characteristics.

The first four questions examine the symptoms of heartburn, acid regurgitation, chest pain, and swallowing trouble in detail. The remaining questions measure the additional upper gut symptoms, respiratory complaints, and health habits.

Symptom frequency was measured on the following scale: 1, none in past year; 2, less than once a month; 3, about once a month; 4, about once a week; 5, several times a week; and 6, daily. Symptoms occurring once a week or more were defined as frequent. Symptom severity was assessed on a four-point scale as follows: mild (can be ignored), moderate (cannot be ignored but does not affect lifestyle), severe (affects lifestyle), and very severe (markedly affects lifestyle).

The QUID score results from the addition of some symptom scores (intensity times frequency of heartburn, regurgitation, chest pain, and dysphagia) or frequencies of other symptoms, such as epigastric/abdominal pain, lump throat, belching, vomiting, hiccup, appetite loss, cough, chest whistles, breathlessness, dyspnea, and hoarseness.

At upper GI endoscopy the presence and severity of esophagitis was rated using the Savary Miller classification [3]:

(1) Grade I-Single or multiple erosions on a single fold
(2) Grade II-Multiple erosions on multiple folds
(3) Grade III-Multiple circumferential erosions
(4) Grade IV-Ulcer, stricture, and esophageal shortening.

Artificial neural networks

We examined the data by means of ANNs [4,5] coupled with an 'evolutionary' algorithm (so called TWIST system, see next paragraph) to identify factors potentially able to distinguish between GERD and healthy individuals or between NERD and EE. The results obtained were then compared with those obtained with the use of classical statistical analysis, that is, LDA or with 'standard' neural networks.

ANNs models were constructed by noncommercial programs developed by Semeion Research Center. Different ANN architectures were assessed in this experiment, but all had the following structure:

(1) the input vector had number of nodes equal to the number of independent variables;
(2) the output vector had two nodes corresponding to the two different outcomes: presence and absence of esophagitis;
(3) one layer of hidden units.

In this study we applied supervised ANNs, to develop a model able to predict with a high degree of accuracy the diagnostic class starting from genotype data alone.

Supervised ANNs are networks which learn by examples, calculating an error function during the training phase

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and adjusting the connection strengths to minimize the error function. The learning constraint of the supervised ANNs makes their own output coincide with the predefined target. The general form of these ANNs is: $y = f(x,w^*)$, where w*constitutes the set of parameters which best approximate the function.

The TWIST system consists of an ensemble of two previously described systems: Training and Testing and Input Selection [6], and select a number of variables that allows highest accuracy in discrimination. The Training and Testing system is a robust data resampling technique that is able to arrange the source sample into sub-samples that all possess a similar probability density function. In this way, the data are split into two or more sub-samples to train, test, and validate the ANN models more effectively. The Input Selection system is an evolutionary wrapper system able to reduce the amount of data while conserving the largest amount of information available in the dataset. The combined action of these two systems allows us to solve two frequent encountered problems when ANNs are implemented.

Both systems are based on a 'genetic' algorithm, the Genetic Doping Algorithm, developed at Semeion Research Centre [7]. The TWIST system is described in detail elsewhere [8].

We used as a benchmark comparator a LDA applied on the same training and testing data sets used for ANNs. For the analysis of LDA, the SAS version 6.04 (SAS Institute, Cary, North Carolina, USA), using forward stepwise procedure, was used.

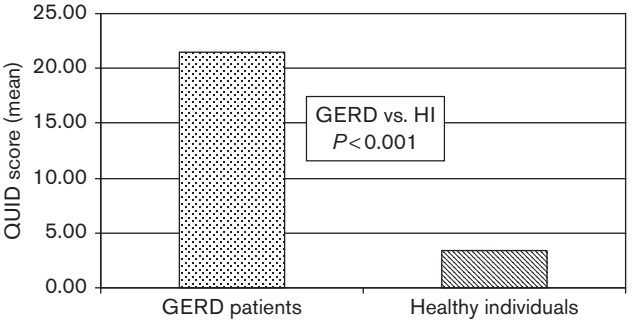
Results

Of the 577 patients recruited, 306 (53%) were diagnosed with esophagitis whereas the remaining 271 (47%) showed no esophageal mucosal damage. The esophagitis severity, assessed by the Savary–Miller classification, was as follows: grade I = 237 (77.5%), grade II = 52 (16.9%), grade III = 9 (2.9%), and grade IV = 8 (2.6%).

The QUID score resulted significantly ($P < 0.001$) higher in GERD patients versus healthy individuals: 21.48 ± 1.55 (SD) versus 3.40 ± 4.18 (SD) (Fig. 1), and similar in EE and NERD patients: 23.17 ± 12.29 (SD) (EE patients) versus 23.41 ± 11.48 (SD) (NERD patients) ($P > 0.05$).

To differentiate GERD patients from healthy individuals, we compared LDA, standard ANNs and the evolutionary TWIST protocol; the last one proved to have greater specificity, sensitivity and accuracy (99.8, 99.1, and 99.2%, respectively) than LDA (99.8, 93.6, and 96.7%, respectively) and standard ANNs (98.3, 93.6, and 96.0%, respectively) (Table 2). The variables selected by the TWIST system for this analysis are listed in Appendix A1. For the purpose of improving the discrimination between EE and NERD patients, we compared each of LDA, the standard ANNs, and the TWIST protocol.

Fig. 1



Mean QUestionario Italiano Diagnostico (QUID) score in gastroesophageal reflux disease (GERD) population and in healthy individuals (HI). For details on QUID questionnaire see text.

As it turned out, the results reached by ANNs, after training 30 neural networks on the variables selected by the protocol TWIST (Appendix A2), were fairly good for the diagnosis of esophagitis (mean accuracy 70.9%) but rather unsatisfactory for the diagnosis of NERD (mean accuracy 62.2%), and similar to what was achieved by LDA and standard ANNs (Table 3).

Discussion

GERD is a highly prevalent condition, affecting 10–30% of the population in the Western countries [9]. Although the diagnosis of GERD, in the absence of alarm symptoms, does not require any diagnostic test to be performed, and is readily made on the basis of symptoms evaluation [10,11], the clinical criteria do not allow us to discriminate among EE, NERD, and functional heartburn. Symptoms indeed are not predictive either of presence/absence of mucosal lesions [12–14] or of presence/absence of functional heartburn, a disorder closely resembling, but not caused by, GERD [15]. Thus, it may become necessary in some cases to perform GI endoscopy or other investigations if the discrimination is clinically relevant, as for example in three broad scenarios: (i) to avoid misdiagnosis, (ii) to identify complications of reflux disease, and (iii) in the evaluation of empirical treatment failures [16]. Moreover, most present guidelines suggest different algorithms for the management of NERD/mild EE patients as opposed to moderate/severe EE patients [10,17], and endoscopy seems to be required to optimize therapy. Finally, in our opinion, the distinction between EE and NERD patients may be of importance since, paradoxically, it is known that EE patients tend to respond better to PPI treatment [18].

In this study we used an ANNs assisted algorithm based on the new QUID questionnaire to improve GERD diagnosis and classification, showing that while the distinction between GERD patients and controls is achieved easily and more precisely, the differentiation between NERD and EE is not satisfactory on the basis of symptom evaluation. This is probably because of the

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Table 2 Diagnostic accuracy of LDA, standard ANNs and ANNs coupled with TWIST protocol to discriminate between GERD patients before therapy and healthy controls

Model	Hidden units	Overall accuracy (%)	Sensitivity (%)	Specificity (%)	ROC AUC	Controls (*N*)	GERD (*N*)	Total (*N*)
LDA	0	96.7	93.6	99.8	0.989	94	577	671
Standard ANNs	4	96.0	93.6	98.3	0.978	94	577	671
TWIST	4	99.2	99.1	99.8	0.999	94	577	671

ANN, artificial neural network; GERD, gastroesophageal reflux disease; LDA, linear discriminant analysis.

Table 3 Diagnostic accuracy of LDA, standard ANNs and ANNs coupled with TWIST protocol to discriminate between EE and NERD patients

Model	EE (%)	NERD (%)	Overall accuracy (%)
LDA	66.2	51.9	59.1
ANNs (53 var)	65.3	57.5	61.4
TWIST (27 var)	70.9	62.2	66.5

ANN, artificial neural network; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; LDA, linear discriminant analysis; NERD, nonerosive reflux disease.

fact that a considerable proportion of NERD patients intermittently develops an EE (progression), even under treatment [19,20] or that the NERD population defined solely on the basis of their symptoms likely include some patients with functional heartburn.

In this study we used the approach based on ANNs to find the best model, based on the questionnaire, to provide the best classification tool to discriminate GERD patients from normal and GERD subgroups (EE vs. NERD) as well.

Similar to our approach, Horowitz *et al.* [21] used ANNs to develop a diagnostic questionnaire for GERD as a diagnostic tool for primary care practitioners. Their symptom score, however, proved to be relatively less sensitive and specific (70–75 and 63–78%, respectively) in the discrimination between GERD and non-GERD. They did not try differentiation between NERD and EE. Other investigators have used different methods, such as the combination of clinical questionnaires and the response to PPI to further categorize NERD patients in endoscopically normal or minimal change patients [22]. They showed, however, that pretreatment symptoms alone do not allow such a differentiation and that not even the response to rabeprazole treatment is helpful in this [22].

In our study we used a more complex approach, namely the use of a novel questionnaire, the QUID, to select the variables and ANNs to use this source of information in an optimal way, that is, to find out the most predictive and relevant items. A GERD symptom questionnaire is at present considered to be useful to improve the diagnosis, to minimize interobserver variability, to facilitate quantitative assessment of patient responses, to capture multiple features of GERD and to save diagnostic money [23]. The characteristics of an ideal GERD questionnaire have been revised by Stanghellini *et al.* [24] and more recently by Fass [25]; among the other features, an optimal questionnaire should: (i) be sensitive in patients with GERD; (ii) cover the frequency and intensity of typical and atypical GERD symptoms; (iii) be multidimensional (cover all symptom dimensions); (iv) have proven psychometric properties (validity, reliability, sensitivity and responsiveness); (v) respond rapidly to change; (vi) be able to be used daily; (vii) be practical and economical; (viii) be patient-assessed; (ix) be easy to understand; (x) be valid in different languages.

Our questionnaire fulfills at least six of the 10 required features for an ideal GERD questionnaire, that is: it is sensitive; it covers the GERD clinical spectrum, it is multidimensional; it is self-addressed; it uses 'real-life' words; it is usable to assess the effect of therapy. As a drawback, QUID is probably a tool best suited for research than for routine clinical practice, because it is rather long (41 items).

As far as the advantages of using the ANNs, during the last 10 years considerable evidence has been provided in the medical literature concerning their role in assisting the diagnostic process [26].

Briefly, they are particularly helpful when the amount of clinical information is high, the interrelationship between complex and possibly non-linear variables, and the traditional statistical approach not completely satisfactory. In the discrimination between NERD and ERD we are precisely in this situation; however, as it turned out, even the most sophisticated ANNs were not able to achieve greater diagnostic accuracy compared to the traditional LDA, contrary to what, for example, is to be observed in other fields of gastroenterology, such as the classification of dyspepsia [27], the assessment of severity of atrophic gastritis [28], the prediction of outcome in acute lower g-i hemorrhage [29] and many others.

Other investigators have tried to classify GERD patients into NERD or EE subgroups on the basis of pretreatment prevalence and type of symptoms, but with unclear results [23].

It must be stressed that in our study we used an ANNs-based questionnaire which was built up using the variables selected in a different sample (out-sample analysis), a process which guarantees us from overfitting the model to the study population and hence the study reflects the true validity of the questionnaire to the clinical practice. The discrepancy in specificity found by others between out-sample and in-sample analysis when the Carlsson–Dent questionnaire was investigated [30] is a clear example of this methodological issue.

In conclusion, our study suggests that our new QUID questionnaire is an interesting tool to differentiate GERD

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patients from healthy control with a high degree of accuracy. On the contrary, the diagnosis of NERD as opposed to EE is not feasible on the basis of symptoms at presentation, not even when the sophisticated tool of ANNs is used. For the time being, 'endoscopic diagnosis is still essential' for the secure recognition of EE, or even Barrett's esophagus [14].

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References

1 Pace F, Buscema M, Dominici P, Intraligi M, Baldi F, Cestari R *et al.* Artificial neural networks are able to recognize gastro-oesophageal reflux disease patients solely on the basis of clinical data. *Eur J Gastroenterol Hepatol* 2005; **17**:605–610.

2 Locke GR, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastrooesophageal reflux disease. *Mayo Clin Proc* 1994; **69**:539–547.

3 Savary M, Miller G. *The esophagus: handbook and atlas of endoscopy.* Solothurn (Switzerland): Verlag Gassman; 1978. pp. 119–159.

4 Cross SS, Harrison RF, Kennedy RL. Introduction to neural networks. *Lancet* 1995; **346**:1075–1079.

5 Baxt WG. Application of artificial neural networks to clinical medicine. *Lancet* 1995; **346**:1135–1138.

6 Buscema M, Grossi E, Intraligi M, Garbagna N, Andriulli A, Breda M. An optimized experimental protocol based on neuro-evolutionary algorithms. Application to the classification of dyspeptic patients and to the prediction of the effectiveness of their treatment. *Artificial Intelligence Med* 2005; **34**:279–305.

7 Buscema M. Genetic doping algorihm (GenD): theory and applications. *Expert Systems* 2004; **21**:63–79.

8 Buscema M, Capriotti M, Bergami F, Babiloni C, Rossini P, Grossi E. the implicit function as squashing time model: a novel parallel nonlinear EEG analysis technique distinguishing mild cognitive impairment and Alzheimer's disease subjects with high degree of accuracy. *Comput Intelligence Neurosci* 2007; **35021**:1–15.

9 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastroesophageal reflux disease: a systematic review. *Gut* 2005; **54**:710–717.

10 Dent J, Brun J, Fendrick AM, Fennerty MB, Janssens J, Kahrilas PJ, *et al.* An evidence-based appraisal of reflux disease management – The Genval Workshop Report. *Gut* 1999; **44** (**Suppl 2**):S1–S16.

11 Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**:1900–1920.

12 Thomson AB, Barkun AN, Armstrong D, Chiba N, White RJ, Daniels S, *et al.* The prevalence of clinically significant upper gastrointestinal findings in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment–prompt endoscopy (CADET-PE) study. *Aliment Pharmacol Ther* 2003; **17**:1481–1491.

13 Rokkas T, Sladen GE. Ambulatory esophageal pH recording in gastro-esophageal reflux: relevance to the development of esophagitis. *Am J Gastroenterol* 1988; **83**:629–632.

14 Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. There are no reliable symptoms for erosive oesophagitis and Barrett's esophagus: endoscopic diagnosis is still essential. *Aliment Pharmacol Ther* 2002; **16**:735–742.

15 Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, *et al.* American Gastroenterological Association medical position statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; **135**:1383–1391.

16 Galmiche JP, Clouse RE, Bálint A, Cook IJ, Kahrilas PJ, Paterson WG, *et al.* Functional esophageal disorders. *Gastroenterology* 2006; **130**:1459–1465.

17 Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, *et al.* New algorithm for the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008; **27**:249–256.

18 Dean BB, Gano AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; **2**:656–664.

19 Pace F, Bollani S, Molteni P, Bianchi Porro G. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD)-a reappraisal 10 years on. *Digest Liver Dis* 2004; **36**:111–115.

20 Labenz J, Nocon M, Lind T, Leodolter A, Jaspersen D, Meyer-Sabellek W, *et al.* Prospective follow-up data from the ProGERD study suggest that GERD is not a categorical disease. *Am J Gastroenterol* 2006; **101**:2457–2462.

21 Horowitz N, Moshkowitz M, Halpern Z, Leshno M. Applying data mining techniques in the development of a diagnostics questionnaire for GERD. *Dig Dis Sci* 2007; **52**:1871–1878.

22 Kusano M, Shirai N, Yamaguchi K, Hongo M, Chiba T, Kinoshita Y; Acid-Related Symptom (ARS) Research Group. It is possible to classify non-erosive reflux disease (NERD) patients into endoscopically normal groups and minimal change groups by subjective symptoms and

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responsiveness to rabeprazole–a report from a study with Japanese patients. *Dig Dis Sci* 2008; **53**:3082–3094.
23 Shaw M. Diagnostic utility of reflux disease symptoms. *Gut* 2004; **53** (**Suppl 4**):25–27.
24 Stanghellini V, Armstrong D, Mönnikes H, Bardhan KD. Systematic review: do we need a new gastro-oesophageal reflux disease questionnaire? *Aliment Pharmacol Ther* 2004; **19**:463–479.
25 Fass R. Symptom assessment tools for gastroesophageal reflux disease (GERD) treatment. *J Clin Gastroenterol* 2007; **41**:437–444.
26 Pace F, Savarino V. The use of artificial neural networks in gastroenterology: the experience of the first 10 years. *Eur J Gastroenterol Hepatol* 2007; **19**:1043–1045.
27 Andriulli A, Grossi E, Buscema M, Pilotto A, Festa V, Perri F. Artificial neural networks can classify uninvestigated patients with dyspepsia. *Eur J Gastroenterol Hepatol* 2007; **19**:1055–1058.
28 Annibale B, Lahner E. Assessing the severity of atrophic gastritis. *Eur J Gastroenterol Hepatol* 2007; **19**:1059–1063.
29 Das A, Wong RCK. Prediction of outcome in acute lower gastrointestinal hemorrhage: role of artificial neural networks. *Eur J Gastroenterol Hepatol* 2007; **19**:1064–1069.
30 Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, *et al.* The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998; **33**:1023–1029.

Appendix

Table A1 Variables selected by TWIST protocol for discrimination between GERD patients and healthy controls

Male
Heartburn frequency
Heartburn intensity
Heartburn at night
Acid regurgitation, presence
Swallowing, difficulty
Swallowing, frequency
Swallowing for solid vs. liquid
Loss of appetite
Cough
Need to raise bed head
Smoking
Heartburn induce by coffee
Instruction level
Job (blue vs. white collar vs. outside work)
Weight
Marital status

GERD, gastroesophageal reflux disease.

Table A2 Variables selected by TWIST protocol for discrimination between EE and NERD patients

Female	Hiccup
Heartburn onset	Appetite
Heartburn improved with antiacids	Cough
Regurgitation frequency	Chest whistles
Regurgitation at night	Dyspnea
Epigastric pain intensity	Smoking (maximum number of cigarette packets)
Swallowing	Smoking (number of cigarette packets/day)
Dysphagia intensity	Coffee (normal or decaffeinated)
Dysphagia severity	Coffee (number of cups/day)
Abdominal pain	Marital status
Regurgitation	Height
Lump throat	Weight
Nausea	Weight variation in the last year
Hematemesis	

EE, erosive esophagitis; NERD, nonerosive reflux disease.

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