The Latent Structure of the Functional Dyspepsia Symptom Complex: A Taxometric Analysis

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Abstract

Objectives Rome III introduced a subdivision of functional dyspepsia (FD) into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), characterized by early satiation/postprandial fullness, and epigastric pain/burning, respectively. However, evidence on their degree of overlap is mixed. We aimed to investigate the latent structure of FD to test whether distinguishable symptom-based subgroups exist.

Methods Consecutive tertiary care Rome II FD patients completed the dyspepsia symptom severity scale. Confirmatory factor analysis (CFA) was used to compare the fit of a single factor model, a correlated three-factor model based on Rome III subgroups and a bifactor model consisting of a general FD factor and orthogonal subgroup factors. Taxometric analyses were subsequently used to investigate the latent structure of FD.

Key Results Nine hundred and fifty-seven FD patients (71.1% women, age 41 ± 14.8) participated. In CFA, the bifactor model yielded a significantly better fit than the two other models (χ^2 difference tests both $p < 0.001$). All symptoms had significant loadings on both the general and the subgroup-specific factors (all $p < 0.05$). Somatization was associated with the general ($r = 0.72$, $p < 0.01$), but not the subgroup-specific factors (all $r < 0.13$, $p > 0.05$). Taxometric analyses supported a dimensional structure of FD (all CCFI < 0.38).

Conclusions & Inferences We found a dimensional rather than categorical latent structure of the FD symptom complex in tertiary care. A combination of a general dyspepsia symptom reporting factor, which was associated with somatization, and symptom-specific factors reflecting the Rome III subdivision fitted the data best. This has implications for classification, pathophysiology and treatment of FD.

Keywords: epigastric pain syndrome, factor analysis, functional dyspepsia, functional gastrointestinal disorders, postprandial distress syndrome, taxometric analysis.

Key Messages

- We studied the latent structure of the FD symptom complex to confirm the existence of the two distinct symptom-based subgroups proposed by Rome III, postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS).
- The FD symptom complex can be described by a bifactor model, i.e. subgroup-specific factors and a general FD factor, the latter of which is associated with somatization.
- Taxometric analysis suggests a dimensional structure of the FD symptom complex, rather than the categorical structure (i.e. subdivision in two distinct subgroups) proposed by Rome III
- These findings have implications for classification, diagnosis, pathophysiology, and treatment of FD

Dyspepsia refers to a symptom complex located in the upper abdomen/epigastrium. In the majority of patients with dyspeptic symptoms, routine clinical and technical investigations do not identify an organic abnormality explaining the symptoms; these patients are referred to as having functional dyspepsia (FD) (1,2). A recent systematic review reported a pooled prevalence of uninvestigated dyspepsia (defined according to Rome II criteria) of 19.0% (95% confidence interval 11.6%-27.7%) (3). FD poses a high financial burden on health systems (4) and is associated with important impairment in health-related quality of life (5). According to Rome III criteria, FD is defined as the presence of chronic (> 3 months) dyspeptic symptoms in the absence of underlying structural or metabolic disease that readily explains the symptoms (1). Four core dyspeptic symptoms are specified: postprandial fullness, early satiation, epigastric pain, and epigastric burning (1). However, other upper gastrointestinal symptoms such as nausea, belching or bloating often co-occur, although belching disorders and nausea and vomiting disorders are classified as separate functional gastroduodenal disorders (1,2). Rome III introduced a subdivision of FD into postprandial distress syndrome (PDS), characterized by early satiation and postprandial fullness, which are typically meal-related, and epigastric pain syndrome (EPS), characterized by epigastric pain and burning, which are assumed to be largely unaffected by meal intake (although EPS symptoms have recently been shown to be aggravated by meal intake too) (6).

The idea of distinct FD subgroups has been raised before by Talley *et al.* (7) who assumed different underlying pathophysiological mechanisms, but also reported important overlap. However, since the introduction of Rome III subgroups, the latent structure of the FD symptom complex, including its dimensional or categorical nature (i.e., the existence of distinguishable subgroups or “taxa”), has not been studied directly. Recent epidemiological studies have provided indirect and mixed evidence on the dimensional or categorical nature of FD. Studies in healthcare-seeking samples showed major overlap between EPS and PDS subgroups, pointing towards a dimensional structure of FD, whereas studies in population-

based samples indicated a good separation of both subgroups, suggesting a categorical structure (8–11). Studies on differential involvement of genetic polymorphisms and pathophysiological mechanisms, including gastric sensorimotor function, immune function, *H. pylori* infection and psychobiological processes in both subgroups have also yielded mixed results (2). Finally, confirmatory factor analyses (CFA) on dyspepsia symptom questionnaires both in the general population and in tertiary care have confirmed the existence of separate but correlated “EPS”, “PDS” and “nausea/vomiting” factors (12–14). However, such a three factor model has never been formally compared to alternative factor structures including one- or bifactor models.

One way to study the latent structure of the FD symptom complex is the application of taxometric methods (15). The idea behind the taxometric method is to identify distinguishable types, or “non-arbitrary categories”, within a dataset (16). This method has, to the best of our knowledge, not been used to study the latent structure of FD, but recent taxometric analyses of medically unexplained symptoms in general favored a dimensional latent structure (17). In the case of FD, this would mean that this construct varies on a continuum which ranges from persons with only a few dyspepsia symptoms of low severity that do not justify a FD diagnosis up to patients who suffer from full-blown dyspepsia with many severe symptoms, rather than a categorical construct characterized by the presence of distinct symptom-based subgroups.

Such a continuum could possibly reflect “somatization”, descriptively defined as the reporting of multiple somatic symptoms for which no organic explanation can be found. It is the most important factor associated with overall FD symptom severity when controlling for other potentially relevant factors including gastric sensitivity and co-morbid depressive symptom severity (18). Further, in a study using structural equation modeling, somatization has been associated with all three symptom factors (EPS, PDS, nausea/vomiting) derived

using CFA (14). However, it should be noted that somatization severity was, on average, not found to be higher in FD compared to organic dyspepsia (19).

Our aim is therefore to investigate the latent structure of FD by means of taxometric analysis to answer the question whether distinguishable symptom-based subgroups (i.e., taxa) of FD exist. Another way to identify such variable groups which may be suitable to distinguish the dyspepsia subgroups is factor analysis. It is important to point out in advance that factor analysis and taxometric analysis should not be seen as competitive methods and do not contradict one another (20). Therefore, we started with a factor analytic approach to investigate the latent structure of FD and to derive applicable indicator sets (i.e., groups of variables) for the subsequent taxometric analyses (21).

Materials and methods

Participants

Consecutive Dutch-speaking patients with a recent Rome II clinical diagnosis of FD [either at their visit to the general GI or GI motility clinic at the University Hospital Leuven (tertiary care) or at a recent secondary care gastroenterologist visit that led to the referral] were asked to complete the Dyspepsia Symptom Severity (DSS) questionnaire (see below) between 1996 and 2009. All patients were included by a single senior gastroenterologist with extensive experience in functional GI disorders (JT), thereby ensuring a consecutive sample recruited from a single tertiary care center. Patients were referred from either primary or secondary care. All patients underwent history taking and clinical examination, upper GI endoscopy, routine biochemistry, and abdominal ultrasound. Inclusion criteria were the presence of symptoms for at least 12 weeks during the last 12 months, in the absence of organic, systemic, or metabolic disease. Symptoms had to be present at least 3 days per week, with two or more symptoms scored as relevant or severe on the DSS questionnaire. Exclusion

criteria were the presence of esophagitis, gastric atrophy, erosive gastroduodenal lesions on endoscopy, heartburn as a predominant symptom, a history of peptic ulcer, major abdominal surgery, and the use of non-steroidal anti-inflammatory drugs or steroids. The study protocol was approved by the University Hospitals Leuven ethics committee prior to the start of patient recruitment.

Assessment of Dyspepsia Symptom Severity and Somatization

We assessed the severity of eight common dyspepsia symptoms (i.e., pain, fullness, bloating, early satiety, nausea, vomiting, epigastric burning, and belching) by means of a four-point Likert scale ranging from 0 (absent) to 3 (severe) using the DSS questionnaire, which has been widely used in previous studies (10,14,17–21, etc).

Somatization was assessed using the PHQ-15, a well-validated self-report questionnaire composed of 15 somatic symptoms, including 14 of the 15 most prevalent DSM-IV somatization disorder criteria. Items are rated on Likert scales (0 to 2). Current level of somatic symptoms (past month) was measured (27). Since this questionnaire became available during the study, data were only collected in a subsample (n=254). Further, since the presence of 3 GI items in the PHQ-15 could artificially inflate the association with DSS and/or one of its underlying factors, we also calculated associations with somatization scores with the 3 GI items excluded (“PHQ-12” as previously used in IBS studies) (28).

Factor Analytic Methodology

CFA was performed with Mplus 7 software (29). We used the weighted least squares with mean and variance adjustment estimation method (WLSMV) in order to account for skewness and kurtosis of the variables. WLSMV estimation method was shown to be very robust with regard to non-normality of the data and yields results similar to the well-known maximum likelihood estimation method (e.g., 24).

The comparative index fit (CFI) and root means square error of approximation (RMSEA) were used to judge the model fit, with a CFI > .95 and a RMSEA < .06 indicating a good fit of the model to the data (31). The model fit based on the comparative fit index (CFI) as an incremental index of fit (i.e., comparison of the actual model with a baseline model) and the root means square error of approximation (RMSEA) as an index of fit which takes into account parsimony of the model (i.e., everything else being equal, the model with less parameters is chosen).

We compared the proposed correlated three-factor model (i.e., PDS factor, nausea/vomiting factor, and EPS factor) with a one factor model as the baseline model and a bifactor model using χ^2 difference tests (*Figure 1*). A bifactor model consists of one general factor (i.e., all items have loadings on this factor) and orthogonal (i.e., uncorrelated) group factors which depict specific variance components distinct from the general factor (e.g., 32).

Taxometric Methodology

Three taxometric methods (MAMBAC, MAXEIG, L-Mode) which are non-redundant in statistical terms were applied (details in *Supplement*) (33).

The comparison curve fit index (CCFI) (34) was applied as an objective measure to compare the empirically observed curve shapes to simulated prototypical dimensional and categorical curve shapes (15). The CCFI can range from 0 (i.e., perfect dimensional structure) to 1 (i.e., perfect categorical structure); the more its value deviates from .50, the stronger the result (34), with values between .45 and .55 being considered ambiguous (15). To depict the results of the taxometric procedures, we plotted two graphs for each analysis: one graph depicting the actual research data in comparison with simulated categorical data and one in comparison with simulated dimensional data. Details are given in *Supplement*.

Results

Participants

Nine hundred and fifty-seven FD patients (71.1% women, age 41 ± 14.8 years, range 13–89) participated. The DSS item and total scores are summarized in *Table 1*. Due to missing values on DSS items, *N* ranged from 932 to 957.

More detailed information, including presence of co-morbid IBS, presumed postinfectious origin of FD, and duration of symptoms, was only available in the subsample in which we obtained data on somatization ($n=254$). The mean age [39.5 ± 12.9 years; range 15–71] and gender distribution (75.3% women) of this subsample did not differ significantly from the full sample. Severity of heartburn (which was excluded as predominant symptom) was available in $n=147$. An overview is given in *Supplementary Table 1*.

Confirmatory Factor Analysis

First, CFA was used to test a *general factor model* consisting of seven FD symptoms loading on one latent factor (G-FD). Based on previous findings of a weak link with other gastroduodenal symptoms (14), and on a close association of this symptom with gastro-esophageal reflux disease (35), belching was excluded from the analysis. The model showed poor fit (*Table 2*).

Second, a *correlated factor model* was specified with three factors found in previous research (12–14): a PDS factor (fullness, bloating and early satiety), a nausea/vomiting factor (nausea and vomiting), and an EPS factor (pain, epigastric burning). Goodness of fit indices were approaching acceptable values, but failed to reach them (*Table 2*). All three factors were significantly and moderately correlated (nausea/vomiting with PDS: $r=.46$; nausea/vomiting with EPS: $r=.41$; PDS with EPS: $r=.43$) suggesting a substantial amount of communality between them.

Third, we tested the *bifactor model* in which every item was allowed to load to both the general factor and one of the three symptom-specific factors reflecting the symptom-based subgroups. This complex model showed adequate fit on CFI, while values on RMSEA were approaching adequacy cut-off scores (*Table 2*). All manifest variables had significant factor loadings on both the general factor and the symptom-specific factors (*Figure 2*). All groups of factors were similar in strength, with at least one symptom loading per factor with value of > .6.

Two χ^2 difference tests were used to compare the models. As expected, the correlated factor model resulted in a better fit than the general factor model $\chi^2(3)=233.09, p<.001$. Moreover, the bifactor model yielded a significantly better fit than the correlated factor model $\chi^2(1)=31.08, p<.001$.

We tested the association between somatization and the different factors in the bifactor model on a subsample. Somatization (as assessed with PHQ-15) was associated with the general symptom factor ($r=0.72, p<0.001$), but not with the symptom-specific factors (all $r<0.13, p>0.05$) (*Figure 3*). The model fit was acceptable: $\chi^2(13)=46.59, p<.001$; RMSEA=0.101 (90%CI: 0.071-0.133); CFI: 0.938; TLI: 0.867. The pattern of associations was similar when the reduced somatization score (excluding the 3 GI items, PHQ-12) was used, although the strength of the association between somatization and the general FD symptom factor was reduced, as could be expected. More specifically, somatization (as assessed with PHQ-12) was associated with the general symptom factor ($r=0.31, p<0.01$), but not with the symptom-specific factors (all $r<0.24, p>0.05$) (*Supplementary Figure 1*). The model fit was acceptable: $\chi^2(13)=47.96, p<.001$; RMSEA=0.103 (90%CI: 0.073-0.135); CFI: 0.931; TLI: 0.851.

Taxometric Analyses

In the graphical summary (*Figure 4*), it is clearly visible that the simulated categorical and dimensional comparison data are of quite different shape in all three procedures. This can be interpreted such that the dataset is appropriate for the taxometric analyses. In line with this expectation, we only observed CCFI values lower than $CCFI = .45$, indicating unequivocal results. Both the results from the three single taxometric analyses (i.e., MAMBAC, MAXEIG, and L-MODE) and the mean CCFI across all procedures (.347) are in favor of a dimensional structure of the data.

A visual inspection of the L-MODE procedure did not reveal any signs of a second mode which should occur in case of a taxometric latent structure. Moreover, the MAMBAC or MAXEIG procedures did not produce any peaked curve which could be interpreted as a sign of an underlying taxometric structure. Further details are given in *Supplement*.

Discussion

We investigated the latent structure of the FD symptom complex to empirically test the Rome III structure which subdivides FD in EPS and PDS, and which classifies nausea and vomiting disorders as a separate category of functional gastroduodenal disorders. From a psychometric perspective, clarifying the latent structure of FD involves information regarding the *type* of latent structure (dimensional vs. categorical), as well as information regarding the exact *model* of the latent structure (number of latent variables, strengths of associations, etc.) (36). We used CFA to specify the best fitting *model* to the latent structure and to derive indicators for subsequent taxometric analyses which was used to decide on the exact *type* of latent structure. The taxometric results suggested a dimensional structure of FD, i.e., no empirical support for qualitatively distinct subgroups of FD was found. This finding is in line with earlier studies demonstrating a large amount of overlap between EPS and PDS in tertiary care (37–40), although percentages of overlap vary among studies and overlap is limited in

primary care (2). Our study adds to the literature by using a novel analysis method to provide statistical confirmation for a lack of qualitatively distinct subgroups of FD.

The initial CFA supported the assumed three-factor structure [i.e., the existence of “PDS”, “EPS” and “nausea/vomiting” factors, which is in line with previous factor analyses on FD symptoms] (12–14). However, it should be noted that the loading of early satiation, one of the two key PDS symptoms, on the “PDS” factor was low compared to the other factor loadings. This was confirmed by exploratory factor analysis (EFA) on this dataset showing a similar loading of early satiation on the “PDS” and “nausea/vomiting” factors (data not shown). This is in line with cross-loadings found for this symptom in a previous study using EFA (13). Our CFA also revealed that, in addition to these distinct symptom factors, a “general (dyspepsia) symptom reporting” factor is necessary to sufficiently describe the data. This finding is in line with the results obtained in irritable bowel syndrome (IBS) (41), where a similar bifactor model offered the best fit to symptom severity data.

Only the general dyspepsia symptom factor was strongly associated with “somatization”. This is in line with earlier results (14) showing that “somatization” was strongly associated with all three dyspepsia symptom subgroup factors in a model which did not include a general dyspepsia symptom factor. Further, this result is in line with a previous study using general linear models to demonstrate that “somatization” is the most important factor associated with overall dyspepsia symptom severity, controlling for other important factors such as depression and gastric sensitivity (18). However, it should be noted that somatization severity was, on average, not found to be higher in FD compared to organic dyspepsia (19). This may suggest that the associations we found here may not be specific to FD, but also apply to organic dyspepsia. Several sources of evidence suggest that “somatization” and, hence, the general dyspepsia symptom factor, are most likely driven by affective processes, which may result in psychological co-morbidity when they go awry. In

FD, for example, somatic symptom levels in general as well as dyspepsia symptom levels in particular are influenced by a complex interaction between early abuse history and psychological traits and states (18,42). More generally, a robust relationship exists between trait negative affectivity and symptom reporting unrelated to physiological dysfunction (43). Further, induction of negative affective states increases somatic symptom reporting in subjects with high levels of “somatization”, including functional somatic syndrome patients (44,45). Finally, functional brain imaging studies have documented the neural mechanisms underlying the affective influences on processing of interoceptive afferent input in functional syndromes (46). Therefore, we conclude that the general dyspepsia symptom factor in the bifactor model may represent a general sensory amplification process that is not specific to particular (groups of) somatic symptoms. This process may in turn be strongly influenced by affective or other central processes.

However, the distinct symptom factors may still be primarily influenced by peripheral mechanisms, particularly abnormalities in gastric sensorimotor function, as these have been shown to be differentially related to different symptom factors (14,23,47–49). Although we found distinguishable FD factors in the CFA, this does not automatically imply the existence of qualitatively distinct subgroups of patients (16,20). Our taxometric analyses did not provide support for the existence of distinct FD subgroups as postulated by Rome III, and it is important to point out that the finding of multidimensionality (i.e., distinguishable FD factors as found in the CFA) should not be mixed up with the existence of qualitatively distinct subgroups of patients (16,20). Paul E. Meehl wrote in his clarifications about the taxometric method it is a “...common error is to think that if factor analysis reveals a big quantitative factor, that refutes the categorical hypothesis. It doesn't, nor does it even argue against it.” (16,20). The factors (i.e., here “nausea”, “PDS”, and “EPS” factors) of a construct (i.e., the dyspepsia symptom complex) represent different facets of the construct but they are still continuous and not categorical. One can think of factor analysis as a tool to identify

symptoms which usually predict one another and therefore built factors. Taxometric analyses, on the other hand, help to identify something that one could call gaps in the distributions of the questionnaire sum scores. Such gaps are likely to be a function of group allocation (i.e., cases of one group belonging to the lower half of the gap and cases of the other group to the upper half of the gap) and, thus, they would be indicative of a taxometric (i.e. categorical) structure.

This study has a number of limitations. *First*, the dyspepsia symptom severity questionnaire we used in the present study was not fully validated. However, the questionnaire has face validity as it is based on severity ratings of 8 key FD/FGD symptoms, has good test-retest reliability (22) and has proven to be useful in both clinical and research contexts (14,18,22–26). *Second*, the results are obtained in tertiary care and can hence not necessarily be generalized to FD in the community, especially as epidemiological data on EPS/PDS overlap show different results in population-based versus clinical samples (2). However, we believe these limitations are outweighed by a number of strengths, including the uniquely large sample size diagnosed with FD according to Rome criteria by a single experienced gastroenterologist, as well as the application of complementary state-of-the-art statistical methods including CFA and taxometric analysis.

In summary, our results provide novel evidence for a dimensional rather than categorical latent structure of the FD symptom complex in tertiary care. Further, CFA showed that a bifactor model, including a combination of a general (dyspepsia) symptom reporting factor, which was associated with somatization, and symptom-specific factors reflecting the subdivision proposed by Rome III, which were not. This has implications for classification, pathophysiology and treatment of FD. Although replication of our results is needed, revisions of the existing classification system (currently Rome III) should take into account that, at least in tertiary care, FD may represent one single rather than two distinct syndromes, as also

suggested by earlier data demonstrating frequent overlap between EPS and PDS in tertiary care (2). However, recent findings indicate that defining PDS based on postprandial nature of symptoms rather than based on distinct symptom profiles per se significantly reduces this overlap (50). Further, our current factor analytical results do identify distinct symptom-based factors corresponding to Rome III subgroups, which may be driven by distinct underlying pathophysiological mechanisms. Therefore, targeting these mechanisms based on symptom profile remains a valid clinical approach warranting the distinction between EPS and PDS, or indeed postprandial and meal-independent symptoms.

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Author contributions: LVO: concept, data analysis, manuscript writing

FJ: concept, data analysis, manuscript writing

MW: concept, data analysis, manuscript review

MW: concept, data analysis, manuscript review

OVdB: concept, manuscript review

JT: patient and data collection, funding, manuscript review

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Supporting information

Detailed information regarding the taxometric methodology and results is provided as online Supplement.

Supplementary Table 1. Descriptive data on the subsample in which somatization data is available ($N = 254$)

Supplementary Figure 1. Bifactor model ($N = 254$) with somatization excluding the 3 GI items (PHQ-12)

Double-headed arrows represent latent correlation coefficients; single-headed arrows represent standardized factor loadings.

All factor loading coefficients indicated in bold are significant at $p < .05$; error terms of manifest variables not shown.

Tables

Table 1. Means (*SDs*) for the items of the Dyspepsia Symptom Severity questionnaire

	<i>N</i>	Mean (<i>SD</i>)
<i>Pain</i>	957	1.43 (1.07)
<i>Fullness</i>	954	1.89 (0.89)
<i>Bloating</i>	949	1.83 (1.13)
<i>Early satiety</i>	949	1.44 (1.09)
<i>Nausea</i>	952	1.35 (1.07)
<i>Vomiting</i>	953	0.69 (1.05)
<i>Belching</i>	954	1.19 (1.03)
<i>Epigastric burning</i>	956	1.04 (1.02)
<i>Total score</i>	932	10.84 (4.31)

Table 2. Goodness of fit statistics for the three different models tested ($N = 957$)

	<i>Model I</i>	<i>Model II</i>	<i>Model III</i>
	<i>1-Factor model</i>	<i>Correlated factor model</i>	<i>Bifactor model</i>
χ^2 (df)	446.67 (14)	121.83 (11)	82.17 (10)
CFI	.763	.939	.960
TLI	.644	.884	.917
RMSEA	.180	.103	.087
90% CI RMSEA	.166–.194	.087–.119	.070 –.105
Evaluation of model fit	Poor	Poor	Adequate

Figure Legends

Figure 1. Overview of the models tested

error terms of manifest indicator variables not shown.

Figure 2. Bifactor model ($N = 957$) with standardized factor loadings

all factor loading coefficients indicated are significant at $p < .05$; error terms of manifest variables not shown

Figure 3. Bifactor model ($N = 254$) with somatization (PHQ-15)

Double-headed arrows represent latent correlation coefficients; single-headed arrows represent standardized factor loadings.

All factor loading coefficients indicated in bold are significant at $p < .05$; error terms of manifest variables not shown.

Figure 4. Averaged L-Mode (top), MAMBAC (middle), and MAXEIG (bottom) plots for the dyspepsia severity questionnaire ($N = 933$).

The plots in the left and right column show the actual research data (bold line) and two thin lines that depict an interval of ± 1 SD either around the expected averaged taxonic (i.e., categorical) (left) or dimensional (right) comparison data.

Figure 1.

Figure 2.

Figure 3.

Figure 4.