Subgroups of IBS patients are characterized by specific, reproducible profiles of GI and non-GI symptoms and report differences in healthcare utilization: A population-based study

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Abstract

Background: In a previous clinical sample of IBS patients, subgroups characterized by profiles of GI and non-GI symptoms were identified. We aimed to replicate these subgroups and symptom associations in participants fulfilling IBS diagnostic criteria from a population-based study and relate them to healthcare utilization.

Methods: An Internet-based health survey was completed by general population adults from United States, Canada, and UK. Respondents fulfilling IBS diagnosis (Rome III and IV) were analyzed for latent subgroups using Gaussian mixture model analysis. Symptom measures were derived from validated questionnaires: IBS-related GI symptoms (Rome IV), extraintestinal somatic symptoms (PHQ-12), and psychological symptoms (SF-8).

Key Results: A total of 637 respondents fulfilled Rome III criteria (average age 46 years, range 18-87, 66% females) and 341 Rome IV criteria (average age 44, range 18-77, 64% female) for IBS. Seven subgroups were identified in the Rome III cohort, characterized by profiles of GI symptoms (constipation-related, diarrhea-related, and mixed, respectively), and further distinguished by the presence or absence of non-GI comorbidities. The Rome IV cohort showed five similar but less distinct subgroups with a preponderance of mixed symptom profiles. Higher severity of non-GI comorbidities was associated with more frequent healthcare visits and medication usage.

Conclusions and Inferences: In line with previous findings in a clinical IBS cohort, we were able to identify population-based subgroups characterized by a combination of GI symptoms with the additional distinction made by varying severity of non-GI symptoms and with differences in healthcare utilization.

KEYWORDS
general population, irritable bowel syndrome, latent profile analysis, mixture model, subgrouping

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain associated with abnormal bowel habits. It is one of the most common functional gastrointestinal (GI) disorders, with an estimated worldwide prevalence of 2%-11%, depending on country and diagnostic criteria used.[1] IBS has a detrimental effect on the quality of life,[2–5] frequently results in work absenteeism,[4] and produces high healthcare costs.[4,6]

IBS patients are currently diagnosed based on the Rome criteria[7,8] (with Rome IV being the latest version), consisting of a combination of symptom-based criteria, which sometimes are supplemented by

diagnostic tests which must show no abnormal findings.[8] The Rome IV criteria require recurring abdominal pain for at least one day per week during the last three months, which is associated with a change in form or frequency of stools and related to defecation.[8] Apart from abdominal pain and altered bowel habits, patients frequently display a variety of other GI symptoms, such as bloating, urgency, and abdominal distention. Additionally, extraintestinal somatic symptoms such as back and joint pain, headaches, sleep disturbances,[9] as well as psychological symptoms, especially anxiety and depression,[9,10] are very common. While not all of these symptoms are present in all patients, those that are present are of high relevance for the overall disease burden of the respective patients and are important for individual treatment decisions.[11] IBS presents as a very heterogeneous disorder and is therefore currently stratified into four different subtypes based on the Rome criteria[7,8]: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U). While the recently updated diagnostic criteria (from Rome III to Rome IV) are considered to be stricter, as they require the presence of abdominal pain (not discomfort) and higher symptom frequency for IBS diagnosis, they have not included substantial changes to the subtyping strategy. This subtyping strategy is based solely on predominant stool consistency and does not take into account other symptoms for classification, despite their relevance for treatment strategies and outcome for the individual patients.[11] It is currently not clear what consequences the updated diagnostic criteria have on the characteristics of the IBS cohort.

While there is a variety of different treatment options available for IBS patients, it is challenging to identify the optimal strategy for the individual. As GI symptoms other than stool consistency, as well as many non-GI symptoms, have shown to be of relevance for optimized individual treatment decisions,[11–14] a need for a more comprehensive stratification approach of patients with IBS remains.

It has also been shown that the healthcare needs of IBS patients not only are associated with the severity of GI symptoms, but are also influenced by extraintestinal and psychological symptoms.[15,16] Therefore, in an era of rapidly rising healthcare costs, there is a need for practical methods to quickly and precisely identify the individual patients' treatment needs.

Aiming to improve the current subtyping options, our group has previously explored methods of stratifying a clinical cohort of IBS patients diagnosed with Rome III criteria, based on combinations of relevant gastrointestinal somatic, extraintestinal somatic and psychological symptoms utilizing advanced statistical techniques.[17] The resulting subgroups were predominantly characterized by specific profiles of GI symptoms (constipation-related, diarrhea-related, and mixed), but further characterized by the presence or absence of a profile of extraintestinal comorbidities, resulting in a six-subgroup solution: (I) constipation with low comorbidities, (II) constipation with high comorbidities, (III) diarrhea with low comorbidities, (IV) diarrhea and pain with high comorbidities, (V) mixed GI symptoms with high comorbidities, and (VI) a mix of symptoms with overall mild severity. These subgroups were identified in healthcare consulters recruited at an outpatient clinic, but it is known that to some extent patients differ from individuals suffering from IBS symptoms without seeking health care (nonconsulters) with regards to illness behavior and coping strategies,[18] and also psychological distress.[19] It is unclear if the six subgroups we identified in a clinical cohort also apply to individuals meeting Rome criteria for IBS in the general population.

In this study, the aim was to validate our previous findings by reproducing these subgroups in a population-based cohort and to compare symptom associations present in respondents fulfilling Rome III criteria for IBS[7] with those present in respondents fulfilling Rome IV criteria for IBS.[8] Furthermore, we hypothesized a higher frequency of healthcare utilization in groups with comorbid non-GI symptoms and aimed to compare the frequency of healthcare utilization between subgroups.

Key Points

- IBS is a heterogeneous disorder. In a clinical sample of IBS patients (Rome III), subgroups defined by specific profiles of GI and non-GI symptom severity were previously identified. We aimed to replicate these subgroups in a population-based study.
- In participants fulfilling Rome III and Rome IV diagnostic criteria for IBS, the subgroups based on a combination of GI and non-GI symptom profiles could largely be replicated. Groups with more severe non-GI symptoms reported higher healthcare utilization.
- This subgrouping approach could facilitate the identification of individual treatment needs and predict healthcare consumption in IBS.

2 | MATERIALS AND METHODS

2.1 | The study cohort

An Internet-based health survey was completed by 6300 general population adults from the United States, Canada, and UK (2100 from each country). The respondents fulfilling IBS diagnosis (Rome IV[8] and III[7]) were analyzed for latent subgroups based on symptom measures derived from validated questionnaires: IBS-related GI symptoms (Rome IV[8]), extraintestinal somatic symptoms (PHQ-12[20]), and psychological symptoms (SF-8[21]).

2.2 | Questionnaire distribution and completion

To collect the data used in this study, a global market survey company (Qualtrics Inc (Provo, Utah, United States)) was assigned with the distribution of the study questionnaire to a nationally representative general population sample of adults from three English-speaking countries: United States, Canada, and United Kingdom.

To ensure that the proportion of sex (50:50), age-groups (40% aged 19-39, 40% aged 40-64%, and 20% aged 65 and older), and education level (maximum 30% with more than sixteen years of formal education) was equal across the countries, quota-based sampling was conducted for the recruitment of participants. The individuals recruited had registered to participate in surveys, such as opinion polls and health studies. Suitable subjects were invited to participate in a "health survey," and to avoid selection bias, no information indicating that the focus of the study was in assessing GI symptoms was given. All participants read and signed an electronic online consent form to accept study enrollment and then completed the survey. Several quality assurance methods were built into the survey to minimize bias and poor quality reporting. These quality assurance methods allowed only one response from each computer device and excluded participants who did not pass attention test questions or were inconsistent in their responses to the three GI diagnostic questions that were presented twice in the survey with the aim of testing consistency of symptom reporting. For more detailed information about this survey, please see Ref.[22–24]

2.3 | Questionnaires

The questions completed by the study participants consisted of validated questionnaires designed to diagnose and measure symptom severity of IBS as well as associated factors such as somatic symptoms and quality of life. The study also contained questions enquiring about age, gender, and ethnicity of the participants. Details are described below.

2.3.1 | GI symptoms: Rome diagnostic questionnaires

The survey contained the complete Rome IV diagnostic questionnaire[8] as well as those questions from the Rome III questionnaire[7] required for IBS diagnosis. The Rome IV questionnaire presents participants with 26-86 questions (depending on skip patterns used if a participant does not have specific symptoms) asking for the frequency and/or severity of FGID-related symptoms. Based on these questionnaires, we determined which participants fulfilled the Rome III and Rome IV diagnostic criteria for IBS,[7,8] respectively (termed Rome III- or Rome IV-positive in the course of this text). To represent the frequency and/or severity of IBS-related GI symptoms in our mixture model analysis, we have used the following questions from the Rome IV questionnaire: "pain frequency" (question 40), "pain after meal" (question 45), "pain severity" (question 46), "hard stools" (question 49), "infrequent stools" (question 51), "straining" (question 52), "incomplete bowel movements" (question 53), "loose stools" (question 59), "urgency" (question 63), and "bloating frequency" (question 65). Pain and bloating frequency are determined using a scale with 9 response alternatives, ranging from "never" to "multiple times per day or all the time," whereas the other questions used an 11-grade scale, ranging from "never (0%)" to "always (100%)." These questions were selected to match the GI questions used in the previous study[17] as closely as possible. The main difference to the previous study was that the Rome IV questionnaire does not contain a question specifically measuring frequent stools.

2.3.2 | Extraintestinal somatic symptoms

The Patient Health Questionnaire (PHQ)-12[20] is a commonly used modification of the PHQ-15,[25] which is a validated measure assessing the severity of somatic symptoms, often referred to as "somatization." The items of the PHQ-12 measure twelve common symptoms as a representation of non-GI or extraintestinal somatic symptoms. Each question uses a scale from 0= "not bothered at all" to 2= "bothered a lot." We used each question as a single-item symptom registration in our mixture model. The questions measure the following symptoms: "back pain," "pain in arms, legs or joints," "pain or problems during sexual intercourse," "headaches," "chest pain," "dizziness," "fainting spells," "feeling the heart pound or race (palpitations)," "shortness of breath," "feeling tired or having low energy (tiredness)," and "trouble sleeping." The question for "menstrual cramps or other problems with the period" was not taken into the analysis due to gender relatedness.

2.3.3 | Psychological symptoms

To measure the severity of psychological distress, we used the Short Form (SF)-8 score,[21] a validated questionnaire commonly used in large-scale epidemiological studies. It measures the general health-related quality of life (QOL) over the past month. We have extracted three questions with Likert-scale answer options from 1 (not at all) to 5 (extremely) to represent psychological symptoms in our mixture model:

1. SF-8-social functioning asking for emotional/physical health:

> During the past 4 weeks, how much did your physical health or emotional problems limit your usual social activities with family or friends?

SF-8-mental health asking for anxiety/depression/stress:

> During the past 4 weeks, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

SF-8-emotional role asking for emotional problems:

> During the past 4 weeks, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

2.3.4 | Healthcare metrics

In addition to the above-mentioned questions, several questions regarding healthcare utilization and treatment were asked. Frequency

of doctor visits (more than once a year or less), as well as doctor visits specifically due to GI problems, was enquired. Weekly use of GI-specific medications (laxatives, antidiarrheal, antiemetics, antacids, and antispasmodics) as well as analgesics (over the counter or prescription) and psychotropic medications (anxiolytics and antidepressants) was assessed. Additionally, subjects were asked about any history of abdominal surgery (cholecystectomy, hysterectomy, appendectomy, bowel resection, as well as an open question regarding any abdominal surgery).

2.4 | Statistical analysis

The statistical analysis was conducted using the R programming language (version 3.3.2—"Sincere Pumpkin Patch")[26] for the mixture model analysis and parts of the multivariate comparisons as well as SPSS (IBM SPSS Statistics for Windows, version 24.0, Armonk, NY, USA; 2016) for univariate and parts of the multivariate comparisons. To conduct univariate comparison of symptom severity between the Rome III- and Rome IV-positive groups, partially overlapping *t*-test were performed using the "partiallyoverlapping" package of R.[27,28]

To stratify the Rome III- and Rome IV-positive participants into subgroups, we conducted a mixture model analysis based on a Gaussian finite mixture model fitted by an expectation-maximization algorithm, in line with the previous analyses conducted by our group on a clinical cohort.[17] The mixture model analysis was performed using the"mclust" package of R[29,30] version 5.3.

Gaussian mixture model analysis is a statistical strategy based on a probabilistic model,[29,31] which stratifies a pooled population into naturally occurring clusters (latent classes, which we will refer to as subgroups in this paper). The basic assumption is that the given dataset is (a) a sample of a larger population and (b) a mix of observations coming from different subgroups, with the aim of the analysis being to identify these subgroups by grouping together observations with similar patterns of variables. To achieve this, the modeling algorithm calculates a large number of subgroups and uses a fit statistic, the Bayesian information criterion,[32] to determine the statistically optimal subgroup solution. Mixture model analysis was conducted after log transformation of the dataset to account for nonparametric distribution.

The resulting subgroups were compared using analysis of variance (ANOVA) with step-down Bonferroni correction for multiple testing where necessary. The respective symptom profiles were visualized in radar plots based on Z-scores (mean and standard deviation of the whole dataset set to zero).

The individual group profiles are termed according to their above-average predominant symptoms (terms as, eg, "high comorbidities" was used if the group average for extraintestinal somatic and psychological symptoms was above average, and the term "low comorbidities" if it was lower than average. Descriptors for individual symptoms were used accordingly).

P-values of <0.05 were considered significant. Results are shown as mean values ± standard deviation (SD) for parametric tests or median and interquartile range for nonparametric tests.

3 | RESULTS

3.1 | Descriptive data of the Rome III-positive and Rome IV-positive study cohorts

The Rome III-positive cohort[7] consisted of 637 subjects. More than half of these were female, and the mean age was 46 (±15.6) years. More than half of the Rome III-positive cohort was characterized as IBS-M subtype. The Rome IV-positive cohort[8] consisted of 341 subjects. Also here more than half were female, and the mean age was 44.5 (±14.6) years. Rome IV subtypes were quite evenly distributed. A majority of participants reported healthcare visits more than once yearly as well as doctor visits specifically for GI problems in both cohorts. GI-specific medications and analgesics were used by around half of respondents, with a higher frequency in the Rome IV cohort. Less than half of the respondents used psychotropic medication. Further details are shown in Table 1.

The Rome IV-positive cohort showed a significantly higher mean severity or frequency of all these symptoms except pain severity and pain associated with meals compared to the Rome III-positive cohort. Details regarding severity/frequency of all symptoms used for the mixture model analysis in both cohorts are shown in Table S1.

3.2 | Mixture model–based subgroups

3.2.1 | Rome III-positive cohort

In this cohort, the best subgroup solution (maximal Bayesian information criterion) was seven subgroups (Figure S1). These seven subgroups were characterized by specific symptom profiles (overview and details in Figure 1, schematic overview in Figure 3A) and termed accordingly:

Two of the groups were characterized by above-average scores for constipation-related symptoms and two by above-average scores for diarrhea-related symptoms and pain. Additional discriminators between these pairs were below-average or above-average scores for extraintestinal somatic or psychological symptoms. These groups were termed constipation-low comorbidities (Figure 1A), constipation-high comorbidities (Figure 1B), diarrhea-pain-low comorbidities (Figure 1C), and diarrhea-pain-high comorbidities (Figure 1D), respectively.

The remaining three groups were characterized by (a) mild severity of all measured symptoms (termed overall mild symptoms group, Figure 1E), (b) a mixed profile of above-average scores for GI, extraintestinal somatic, and psychological symptoms (termed mixed-high comorbidities, Figure 1F), and (c) above-average scores for psychological symptoms and mild severity for all GI and extraintestinal symptoms except tiredness (termed psychological symptoms subgroup, Figure 1G). A schematic overview is presented in Figure 4A.

Differences in the respective group scores were significant for all analyzed symptoms in an ANOVA test after stepdown Bonferroni correction (Table S2).

TABLE 1 Demographic data and healthcare metrics in the Rome III-positive and Rome IV-positive cohort

		Rome III-positive cohort		Rome IV-positive cohort	
	Number	**637**		**341**	
Demographics	Age (mean ± SD)	46 ± 15.6		44.5 ± 14.6	
	-	Count	Percentage	Count	Percentage
	Female	420	65.9%	217	63.6%
	Male	217	34.1%	124	36.4%
Rome subtypes	IBS-C	106	16.6%	95	27.9%
	IBS-D	131	20.6%	117	34.3%
	IBS-M	383	60.1%	113	33.1%
	IBS-U	17	2.7%	16	4.7%
Healthcare utilization	More than once yearly healthcare visits	481	75.5%	274	80.4%
	Doctors visit due to GI problems	370	58.1%	227	66.6%
Medication taken at least once weekly	GI-specific medication	351	55.1%	227	66.6%
	Analgesics	342	53.7%	222	65.1%
	Psychotropic medicine	227	35.6%	150	44.0%
	Any of the above medication	492	77.2%	293	85.9%
Previous surgery	Abdominal surgeries	242	38.0°%	153	44.9%

3.2.2 | Rome IV-positive cohort

In the Rome IV-positive cohort, the maximal Bayesian information criterion was achieved for a five-subgroup solution (Figure S2). Of these subgroups, one was characterized predominantly by constipation-related GI symptoms with additional above-average psychological symptoms and was termed constipation-predominant subgroup (Figure 2A). Another subgroup was characterized predominantly by pain and diarrhea-related GI as well as psychological symptoms and termed diarrhea-pain-predominant subgroup (Figure 2B). The other three groups were characterized by a mix of symptoms and set apart by the severity of the respective symptom profiles: The mixed-high psychological symptoms subgroup (Figure 2C) showed a mostly high symptom severity and especially high psychological symptoms but low intercourse-related pain/problems, while the mixed-moderate psychological symptoms group (Figure 2D) showed a similar profile but moderate psychological symptoms and high intercourse-related pain/problems. The overall mild symptoms group showed below-average scores for all symptoms (Figure 2E). A schematic overview is presented in Figure 3B.

Differences in the respective group scores were significant for all analyzed symptoms in an ANOVA test after stepdown Bonferroni correction (Table S3).

3.3 | Further group characteristics

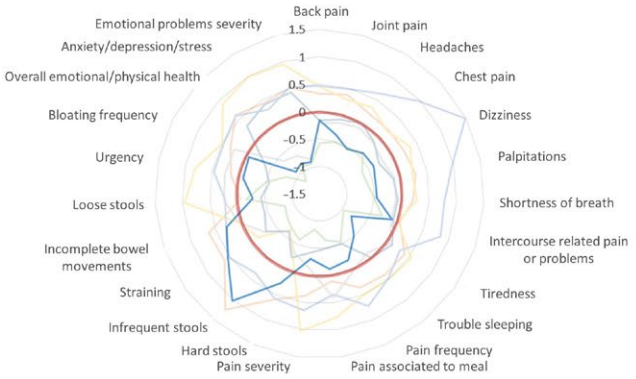
In both cohorts, all subgroups showed a higher percentage of females, with no statistically significant differences between the groups regarding gender distribution. The highest mean age was seen in the overall mild symptoms subgroups of both cohorts ($P < 0.01$ in both between-group comparisons). IBS-C and IBS-D were present to a greater extent in the constipation- and diarrhea-pain-predominant subgroups, but not limited to these, while IBS-M and IBS-U were distributed evenly among all groups except the diarrhea-pain-predominant group of the Rome IV-positive cohort which mostly contained IBS-D ($P < 0.01$ in both between-group comparisons, Figures 4 and 5).

In the high-comorbidities groups of both cohorts, health care was utilized more frequently compared to the other groups ($P < 0.01$ in both between-group comparisons). In the Rome III-positive cohort, group differences were also significant regarding doctor visits specifically for GI problems ($P < 0.01$), which was more evenly distributed in the Rome IV cohort. Groups with high non-GI comorbidities reported more medication use in both cohorts ($P < 0.01$ in both between-group comparisons). There were no statistically significant differences between the groups with regards to abdominal surgeries. Details are presented in Figures 4 and 5.

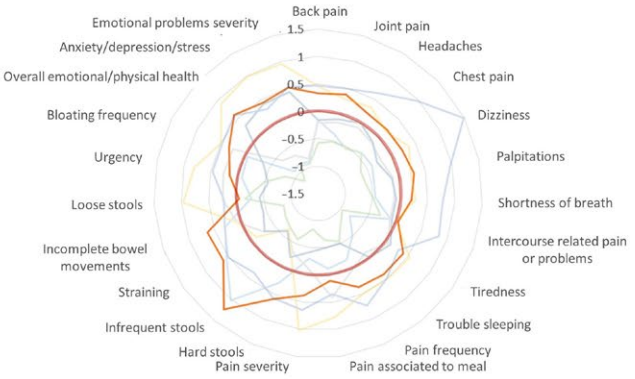
4 | DISCUSSION

In this study, the subgroups previously identified in a clinical Rome III IBS cohort could largely be reproduced in a population-based sample of individuals meeting Rome criteria for IBS. The previously seen symptom profiles were fully reproduced in the population-based Rome III IBS cohort, where all six subgroups with corresponding

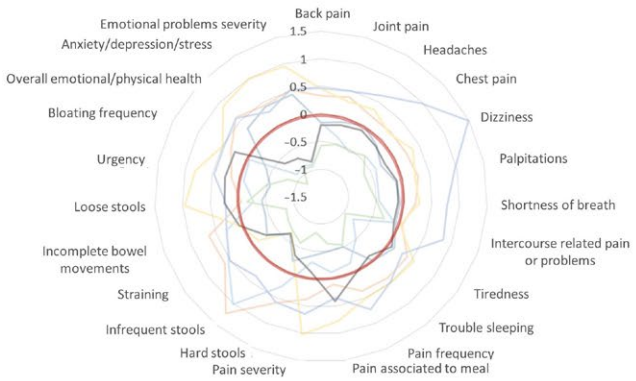
(A) Constipation-low comorbidities



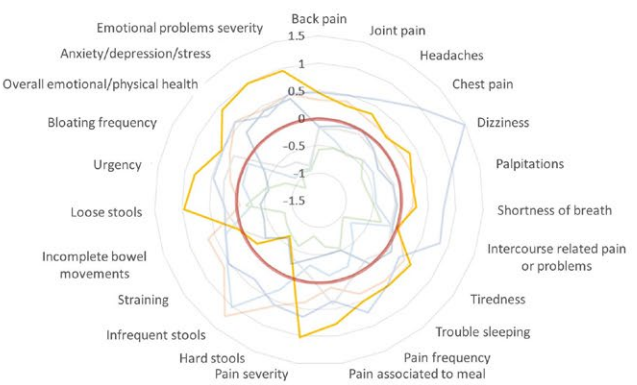
(B) Constipation-high comorbidities



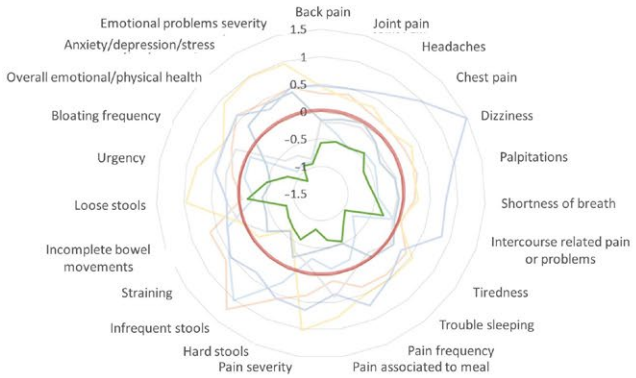
(C) Diarrhea-pain-low comorbidities



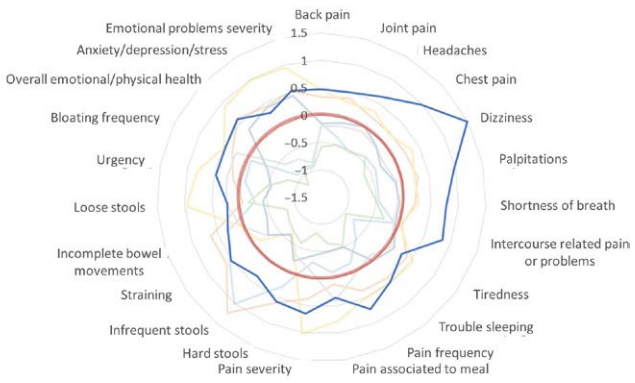
(D) Diarrhea-pain-high comorbidities



(E) Overall mild severity



(F) Mixed GI-high comorbidities



(G) Psychological symptoms

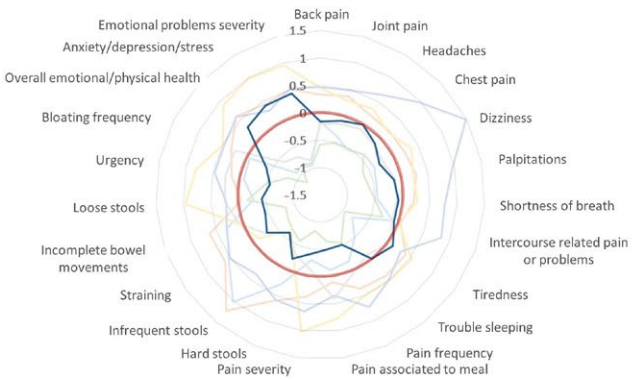


FIGURE 1 A-G, Detailed symptom profiles of the seven subgroups identified in the Rome III-positive cohort. The group averages are standardized and plotted in relation to the cohort average that is normalized to zero. Values above zero are thus above average, by which the group symptom profile can be determined. The average is marked with a dark-red circle for easier determination of above- and below-average severity of the respective symptoms. In each panel, the respective groups' profile is highlighted in color and the remaining group profiles are kept in gray in the background. As the symptom "Fainting spells" was only present in a few respondents, it was removed from this plot to improve comparability of the remaining symptoms

symptom profiles were identified, as well as an additional seventh group. In the population-based Rome IV IBS cohort, five subgroups with symptom profiles partly corresponding to the clinical paragon were identified, but with a preponderance of mixed symptom profiles. Like the subgroups of the clinical sample, the population-based subgroups were characterized by a combination of GI symptoms with the additional distinction made by varying severity of non-GI symptoms. Members of subgroups with high extraintestinal and psychological symptoms reported higher frequency of healthcare utilization and medication usage, but not more abdominal surgeries.

Due to the heterogeneity of IBS, there is a long-standing history of stratification efforts (most importantly in Rome II-IV criteria[7,8,33]), but these have focused solely on stool consistency. In a previous attempt to improve stratification of this complex disorder, our group created a classification approach[17] that takes into account a comprehensive set of GI, extraintestinal somatic, as well as psychological symptoms. To estimate the validity of this approach, we proposed three requirements to be tested[34]: reproducibility, potential differences in underlying pathophysiology, as well as whether group membership could be utilized as a predictor for treatment outcome. In the here presented study, we have, as a first step, explored the reproducibility of the subgroups.

We have first tested this reproducibility in a Rome III-defined cohort,[7] as the clinical paragon[17] was also based on a Rome III-defined cohort.[7] In this Rome III-positive population-based cohort, we successfully reproduced all groups and symptom associations previously described in the clinical patient cohort,[17] with the addition of a group predominantly displaying psychological symptoms. These subgroups therefore seem to be present both in IBS patients and in a population-based cohort fulfilling Rome III diagnostic criteria for IBS and have now been identified in cohorts from Sweden (clinical cohort[17]) as well as the USA, UK, and Canada (population-based cohort; the present study). This highlights a high level of reproducibility of these subgroups, supporting the validity of this subgrouping approach.

In light of the recent publication of the Rome IV criteria,[8] we have also looked into subgroups and symptom associations in patients fulfilling these criteria and found similar but less distinct symptom associations. This is an outcome which may be expected given the change of diagnostic criteria and may be the result of a stricter selection of qualifying individuals due to the changes in symptom frequency thresholds utilized for diagnosis, as well as the removal of the symptom "discomfort." These more selective criteria likely lead to a generally higher symptom severity in the Rome IV cohort (which was observed in this study, especially for non-GI symptoms) and thus a more homogenous cohort. As our statistical approach determines subgroups based on the relative severity of a profile of symptoms, overall high scores will lead to fewer, less distinct groups, just as observed. An additional noteworthy difference from the previous Rome III questionnaire is the removal of specific questions assessing frequent bowel movements, which may explain why three of the identified groups were characterized by a mix of GI symptoms rather than diarrhea or constipation.

Consistent with previous studies which showed extraintestinal symptoms to be of high relevance for the frequency of doctor visits,[9–11,13,14,16] our study observed more frequent healthcare utilization and medication usage in the groups showing above-average extraintestinal somatic and psychological symptom severity. This further supports the importance of recognizing and considering these symptoms in clinical decision-making to enable individualized treatment strategies for these patients, as previously suggested by use of a multidimensional clinical profiling strategy.[11,35] Adding the relevant non-GI symptoms to future IBS subtyping approaches may facilitate quicker and more comprehensive assessment of these symptoms and may therefore improve classification. While this seems relevant for the Rome III cohort, our results suggest that this may be even more important in the Rome IV cohort, where prominent non-GI symptoms were generally observed.

Currently, IBS is viewed as a multifactorial disorder, with various pathophysiological mechanisms identified.[36,37] However, not all of these mechanisms seem to be of relevance for all patients.[36,37] This hypothesis of multiple etiologies as opposed to multifactorial genesis has been gaining increasing support in the field of IBS research,[9,37] and the symptom associations described here could potentially aid in identifying distinct underlying mechanisms. An important finding in this regard is the association of above-average scores for diarrhea with above-average scores for pain, which has consistently been observed in all cohorts.[17] This recurrent pattern may suggest a common denominator between these symptoms and may therefore point toward a common etiology, a hypothesis that needs to be carefully evaluated in future studies. Our results also support the high importance of comprehensive clinical phenotyping to reduce heterogeneity and dissimilarity of patients. The potential presence of different endotypes needs to be accounted for when studying underlying mechanisms, and detailed phenotype-based subgrouping such as suggested in this study may aid in identifying relevant mechanisms by enabling more quick and comprehensive screening for relevant symptoms.

This study is the first to utilize these advanced statistical methods to analyze latent structures for subgroups and symptom associations in a large numberof adult individuals from the general population and relating these symptom associations to healthcare usage. By utilizing an Internet-based survey for data collection, we were able

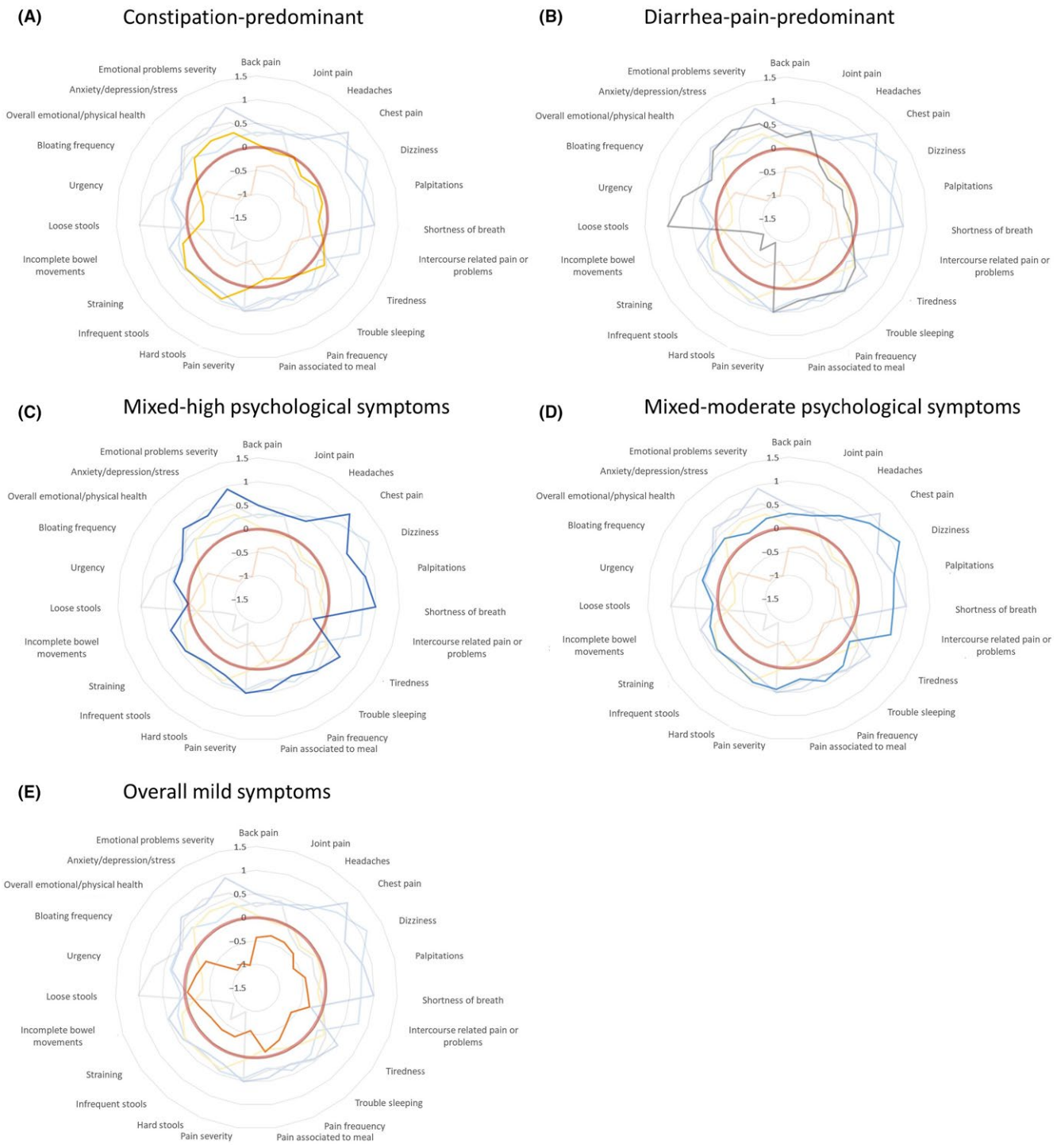


FIGURE 2 A-E, Detailed symptom profiles of the five subgroups identified in the Rome IV-positive cohort. The group averages are standardized and plotted in relation to the cohort average that is normalized to zero. Values above zero are thus above average, by which the group symptom profile can be determined. The average is marked with a red circle for easier determination of above- and below-average severity of the respective symptoms. In each panel, the respective groups' profile is highlighted in color and the remaining group profiles are kept in gray in the background. As the symptom "Fainting spells" was only present in a few respondents, it was removed from this plot to improve comparability of the remaining symptoms

to generate a dataset that corresponded to the demographics of the general population in the respective countries. Built-in quality checks, such as automatic checks for missing or meaningless responses as well as checks to identify and exclude low-quality respondents, were applied to ensure high-quality data. This study design has, in recent years, become increasingly popular,[38] and several recent studies focusing on GI symptoms with this type of methodology have been published.[22,23,39–41] This development has been

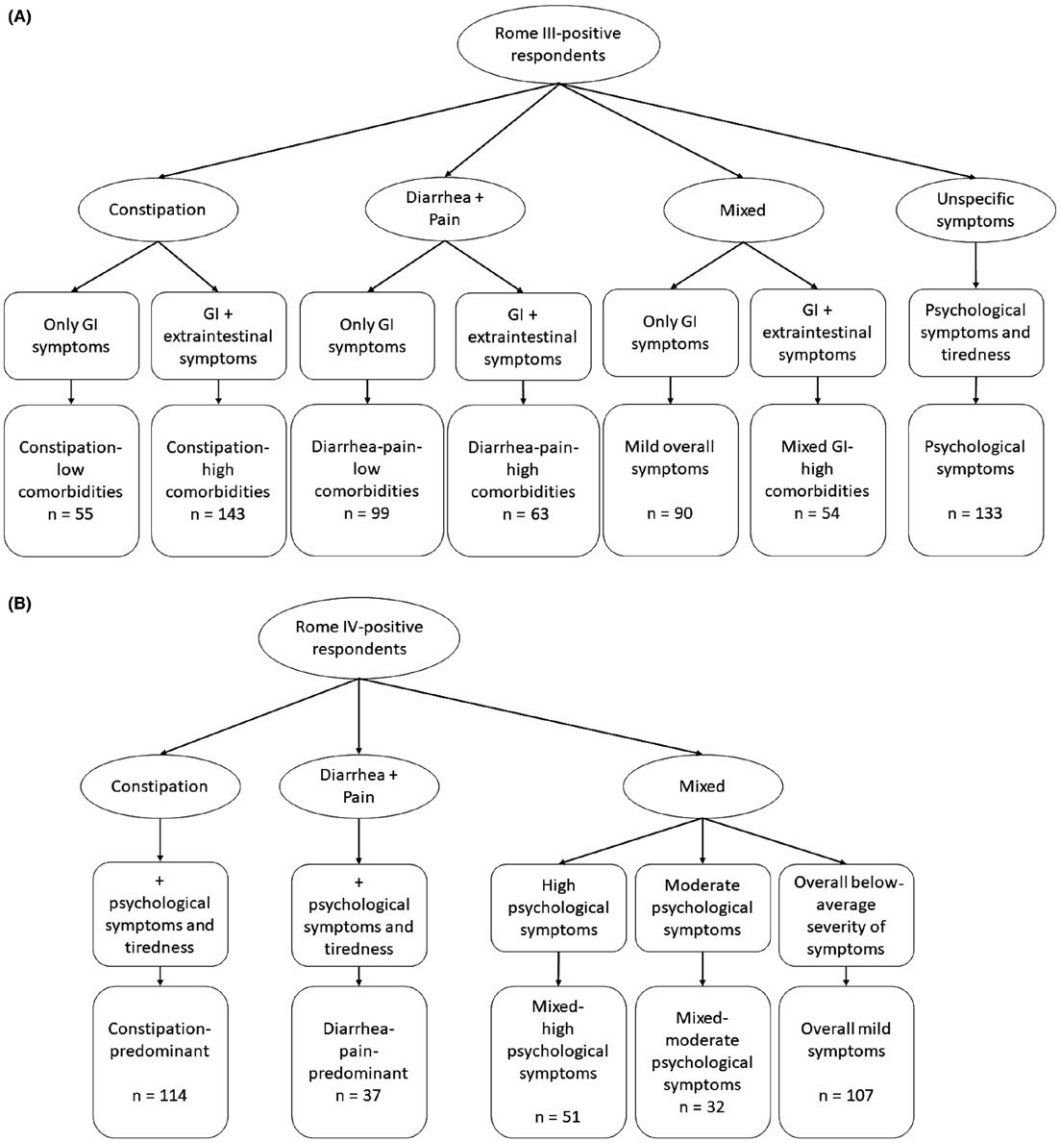


FIGURE 3 Schematic overview over the characteristics of the latent subgroups present in A) the Rome III- and B) Rome IV-positive cohort, respectively

made possible by the near-ubiquitous availability of Internet access in Western countries,[42] minimizing the risk of recruitment bias due to Internet accessibility.

Nevertheless, some limitations need to be considered when interpreting the results:

It is possible that respondents of Internet surveys are different from those individuals not willing to participate in such surveys regardless of age, sex, etc, but there is little evidence of this to this date. Various previous studies focusing on several different healthcare questions have shown that Internet surveys produce comparably reliable results as traditional survey strategies for assessing epidemiological measures.[38] We therefore cannot find strong arguments contradicting the generalizability of our results due to potential recruitment bias.

It is important to consider that this study was performed in Western countries, and global generalizability may be limited; therefore, further studies are needed to test for reproducibility in non-Western countries. Nevertheless, the fact that we were able to reproduce our previously published subgroups in this large cohort provides a strong argument for the relevance and generalizability of these subgroups.

The present study had a cross-sectional design, which needs to be considered. It is known that IBS symptoms fluctuate over time,[43–45] so it is unclear how stable the subgroup membership of an individual is. Presumably, the usage of a comprehensive set of symptoms may aid in a higher longitudinal stability, but the subgroups described here need to be subjected to further studies regarding longitudinal stability of group membership as well as predictive abilities regarding underlying mechanisms and treatment outcome.

In conclusion, we have identified subgroups based on a comprehensive set of IBS-related symptoms in a population-based study.

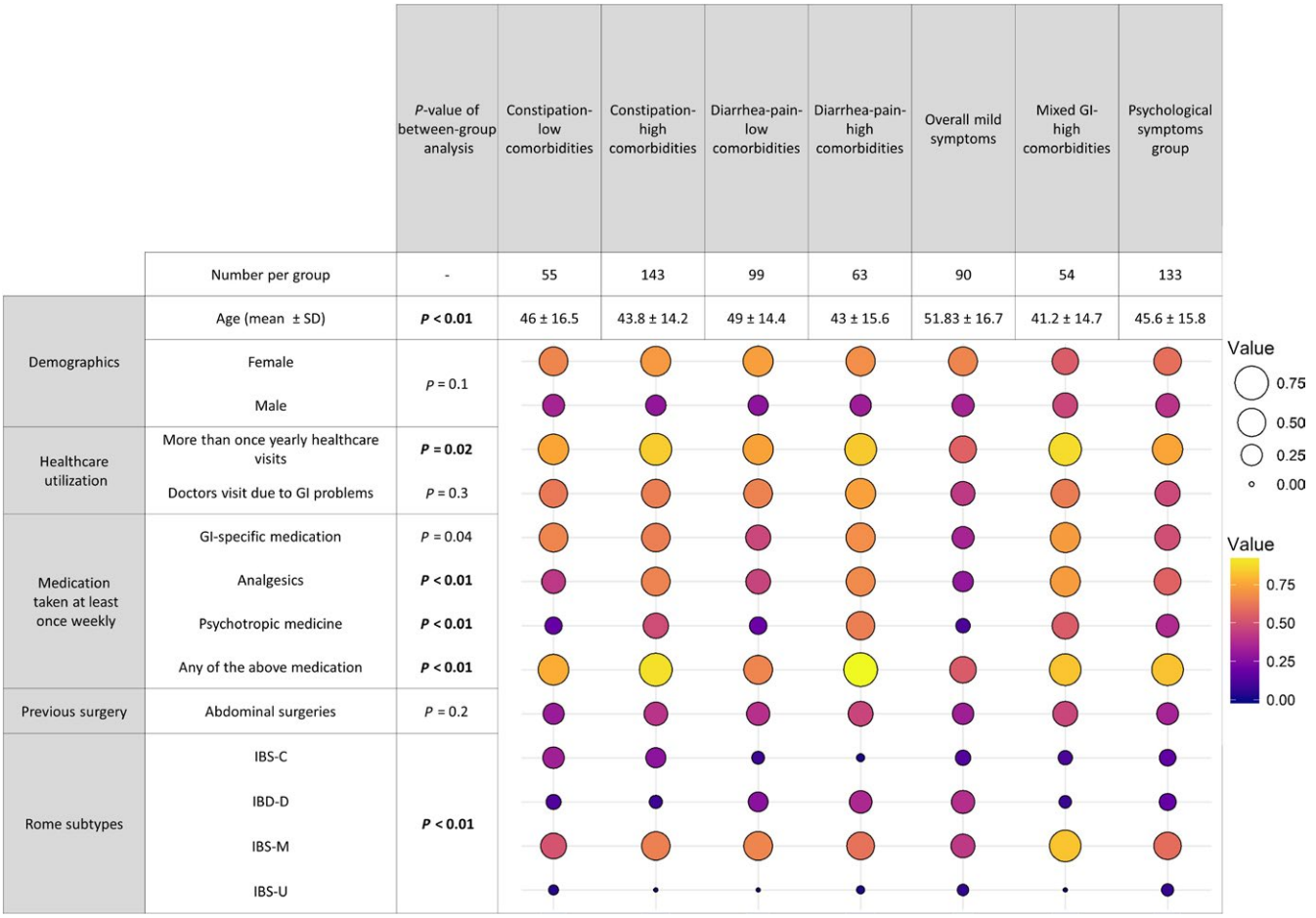


FIGURE 4 Further characteristics and differences of healthcare metrics between the subgroups identified in the Rome III-positive cohort. The balloon plot shows the percentage of respondents of each subgroup that have chosen the respective answer. The larger and more yellow the balloon, the more the group members have marked this answer

These subgroups were defined by predominant GI symptoms and additionally by the respective severity of non-GI symptoms, in line with previous findings in a clinical cohort.[17] Subgroups with elevated non-GI symptoms showed more frequent healthcare utilization and medication usage, suggesting that screening for these additional symptoms in IBS patients may aid clinicians in identifying those where gut-directed therapeutic approaches may be sufficient as opposed to those that might benefit from therapies targeting extraintestinal somatic and psychological symptoms as well. Future studies are needed to further explore the reproducibility of these subgroups in other cohorts and test the association of these specific symptom profiles to pathophysiological mechanisms as well as the suitability of these subgroups for predicting treatment outcome.

DISCLOSURE

AP and LÖ had no competing interests. OP received salary support from research grants from Takeda Pharmaceuticals and Salix Pharmaceuticals and from a consulting agreement with Ironwood Pharmaceuticals and an educational grant provided by Takeda Pharmaceuticals, and received a speaker honorarium in an educational program supported by Ironwood Pharmaceuticals and Takeda Pharmaceuticals. HT served as consultant/Advisory Board member for Almirall, Allergan, and Shire. AS served as a consultant and speaker for Takeda Israel. WEW received research grants from Takeda, Ironwood, Salix, and the Rome Foundation; served as a consultant to Biomerica, USA, Ono Pharmaceuticals, and Ferring; and received unrestricted educational grants from Takeda and Ferring. MS received unrestricted research grants from Danone and Ferring Pharmaceuticals; served as a consultant/Advisory Board member for AstraZeneca, Danone, Nestlé, Almirall, Allergan, Albireo, Glycom, and Shire; and served as a speaker for Tillotts, Menarini, Takeda, Shire, Allergan, and Almirall.

AUTHOR CONTRIBUTIONS

Guarantor of the article: Magnus Simrén.

Specific author contributions: OSP and WEW contributed to the study design, questionnaire development, execution of survey, data processing, and manuscript editing; ADS contributed to the study design, questionnaire development, and manuscript editing;

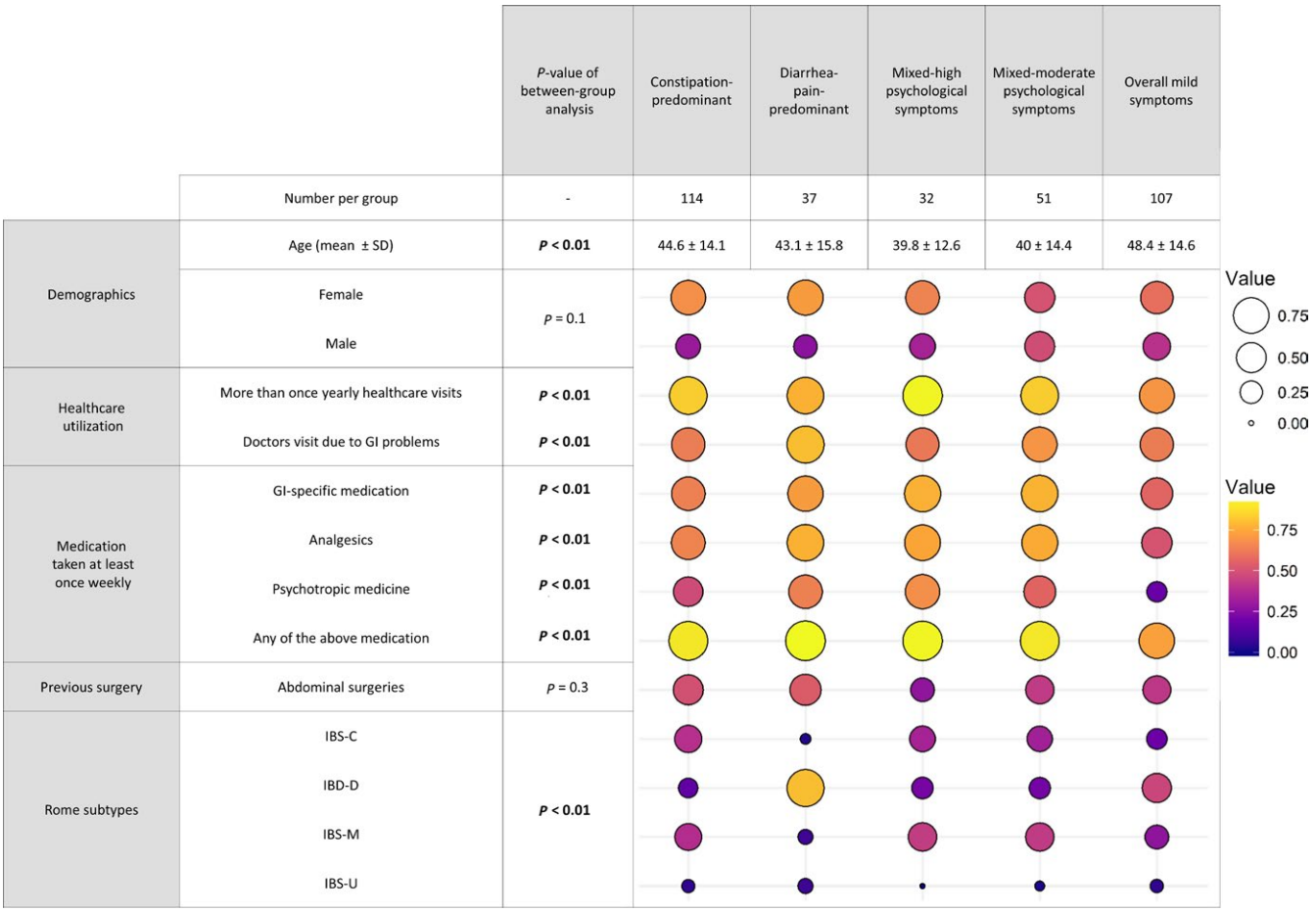


FIGURE 5 Further characteristics and differences of healthcare metrics between the subgroups identified in the Rome IV-positive cohort. The balloon plot shows the percentage respondents of each subgroup that have chosen the respective answer. The larger and more yellow the balloon, the more the group members have marked this answer

HT and LÖ contributed to interpretation of data and manuscript editing; MS contributed to study design, interpretation of data, and manuscript editing; AP developed the analytical strategy, performed all analyses, interpreted the data, and wrote the manuscript; and all authors reviewed and approved the final version of the manuscript.

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