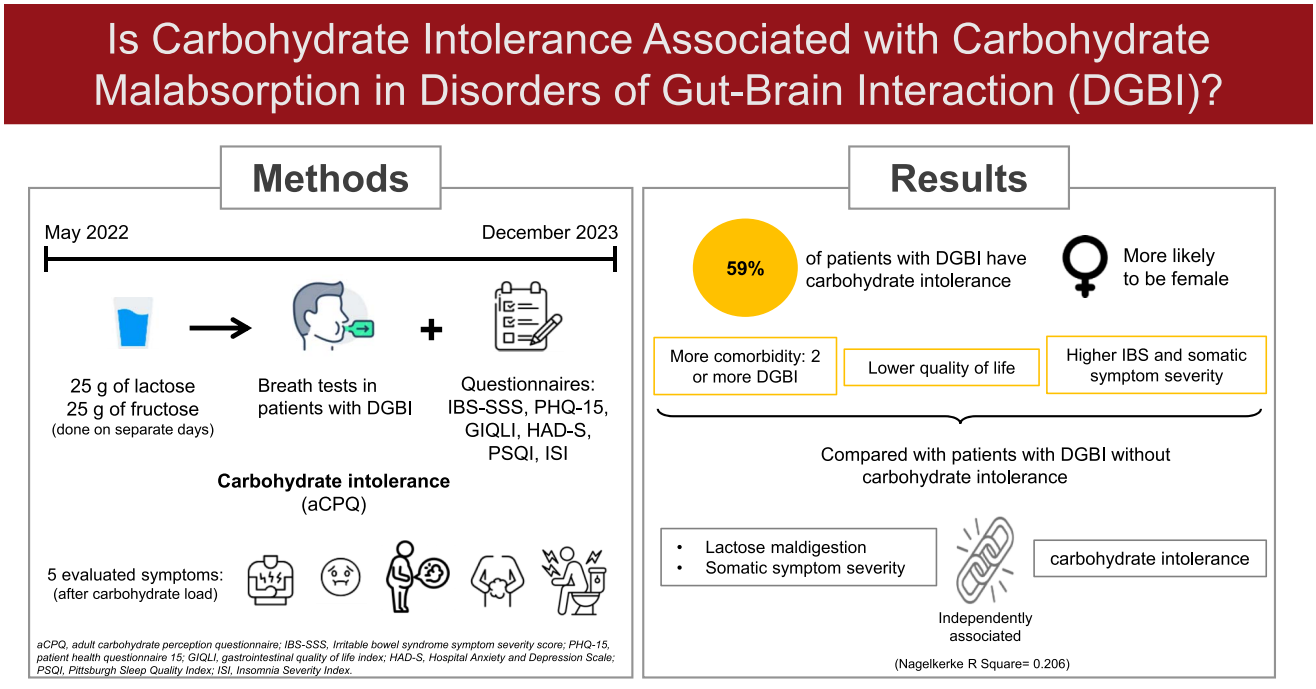
# Is Carbohydrate Intolerance Associated With Carbohydrate Malabsorption in Disorders of Gut-Brain Interaction?

Hiba Mikhael-Moussa, MSc[1], Charlotte Desprez, MD, PhD[1,2], André Gillibert, MD, PhD[3], Anne-Marie Leroi, MD, PhD[1,2], François Mion, MD, PhD[4], Guillaume Gourcerol, MD, PhD[1,2] and Chloé Melchior, MD, PhD[1,5]

INTRODUCTION: **We aimed to explore the prevalence of carbohydrate (lactose and fructose) intolerance in patients with disorders of gut-brain interaction (DGBI) and to characterize those patients regarding gastrointestinal and nongastrointestinal symptoms.**

METHODS: **Patients with DGBI who were referred to the physiology unit of our hospital between May 2022 and December 2023 for lactose (25 g) and fructose (25 g) breath tests were prospectively included. Patients were required to have a negative glucose breath test, before lactose and fructose breath tests, and to have completed the adult carbohydrate perception questionnaire during each breath test. Intolerance was defined as an increase of ≥20 mm in the Visual Analog Scale score from baseline in at least 1 of the 5 symptoms (pain, nausea, bloating, flatulence, and diarrhea) assessed with the adult Carbohydrate Perception Questionnaire.**

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[1]Univ Rouen Normandie, INSERM, Normandie Univ, ADEN UMR1073, Nutrition, Inflammation and Microbiota-Gut-Brain Axis, Rouen, France; [2]Department of Physiology, CIC-CRB 1404, CHU Rouen, Rouen, France; [3]Department of Biostatistics, CHU Rouen, Rouen, France; [4]Hospices Civils de Lyon, Université Lyon 1, Digestive Physiology Department, Hôpital Edouard-Herriot, Lyon, France; [5]Department of Gastroenterology, CIC-CRB 1404, CHU Rouen, Rouen, France.
**Correspondence:** Hiba Mikhael-Moussa, MSc. E-mail: hiba.mikhael-moussa@univ-rouen.fr.
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RESULTS: **Among the 301 patients with DGBI included in our analysis, 178 (59.1%) had carbohydrate intolerance. Carbohydrate-intolerant patients were significantly more likely to be female (*P* value < 0.001), to have 2 or more DGBI (*P* value = 0.001), to have lactose maldigestion (*P* value< 0.001) and fructose malabsorption (*P* value = 0.023), higher irritable bowel syndrome and somatic symptom severity, and lower quality of life (*P* value < 0.001) compared with patients without carbohydrate intolerance. The binary logistic regression showed that lactose maldigestion (*P* value = 0.001), as well as somatic symptoms (*P* value = 0.025), were independently associated with carbohydrate intolerance (Nagelkerke R Square = 0.206).**

DISCUSSION: **Carbohydrate intolerance affects a substantial group of patients with DGBI, affecting their quality of life and symptom severity. Further research is needed to explore the underlying mechanisms in patients who do not have carbohydrate malabsorption/maldigestion.**

**KEYWORDS:** carbohydrate intolerance; lactose maldigestion; fructose malabsorption; adult Carbohydrate Perception Questionnaire; disorders of gut-brain interaction

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/D635, http://links.lww.com/AJG/D636

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## INTRODUCTION

Patients with disorders of gut-brain interaction (DGBI) often experience food-related symptoms (1,2). It could result from various mechanisms, including food maldigestion/malabsorption and intolerance, especially of carbohydrates (3).

Understanding the difference between malabsorption, maldigestion, and intolerance is crucial. Malabsorption refers to the incomplete or failed absorption of nutrients (e.g., fructose) in the small intestine. When larger nutrient molecules (e.g., lactose) are involved, we talk about maldigestion, as digestion precedes nutrient absorption. Bacterial fermentation of unabsorbed carbohydrates in the colon produces short-chain fatty acids and gases. Carbohydrate maldigestion/malabsorption can therefore be diagnosed using breath tests (4). The occurrence of gastrointestinal symptoms after carbohydrate ingestion is referred to as carbohydrate intolerance. The mechanisms behind carbohydrate intolerance are not fully understood, they can occur in the presence of malabsorption because of an increase in gas ($H_2$ and $CH_4$) production in the colon or in cases of bacterial fermentation in the distal small intestine, also named small intestinal bacterial overgrowth (5,6). However, carbohydrate intolerance can also arise in some cases in the absence of malabsorption, suggesting the role of visceral hypersensitivity, or because of rapid oroanal transit (7–9).

Nowadays, routine testing for carbohydrate malabsorption in patients with DGBI is not recommended (10,11). Nevertheless, the evaluation of symptoms in patients with DGBI after carbohydrate ingestion seems important for an improved management, but when it comes to carbohydrate intolerance evaluation in DGBI, studies are very heterogeneous using different assessment methods (12–14).

Therefore, in this study, we aim to explore the prevalence of carbohydrate (lactose and fructose) intolerance in patients with DGBI and to characterize those patients regarding malabsorption/maldigestion, gastrointestinal, and nongastrointestinal symptoms.

## MATERIALS AND METHODS

### Patients

We included patients who have already been diagnosed with DGBI (by their physician after the exclusion of organic disorders) referred to the outpatient clinic of the Physiology Unit of Rouen University Hospital (France) between May 2022 and December 2023. To be included, patients needed to have completed carbohydrate breath tests for both lactose and fructose, along with a symptom assessment using adult Carbohydrate Perception Questionnaire (aCPQ) (15,16).

The inclusion criteria were to be 18 years or older and to test negative on a 75 g glucose breath test (performed before lactose and fructose breath tests, according to our method previously described) to reduce the possibility of small intestinal bacterial overgrowth as recommended by the European guidelines, which could result in false-positives on lactose and fructose breath tests (4,17). Patients also completed several validated questionnaires on their diagnoses (Rome IV), irritable bowel syndrome (IBS) symptom severity (IBS-SSS), somatic symptom severity (Patient Health Questionnaire-15), quality of life (Gastrointestinal Quality of Life Index), anxiety and depression levels (Hospital Anxiety and Depression Scale), sleep quality and insomnia (Pittsburgh Sleep Quality Index and Insomnia Severity Index), and relevant demographic information was collected (see Supplementary Data, http://links.lww.com/AJG/D635) (18–24). Patients were also asked if they were following a lactose-free diet. The presence of diabetes was also assessed.

All patients gave their written informed consent and are part of the cohort from the research protocol "OBSERVATOIRE DES PATIENTS SOUFFRANT DE TROUBLES FONCTIONNELS INTESTINAUX," which was approved by the ethical review board in 2019 (N° ID-RCB: 2017-A02134-49).

### Clinical assessment

***Carbohydrate intolerance and malabsorption assessment.*** All breath tests were executed and interpreted according to the European guidelines on hydrogen and methane breath tests, (specific instructions in Supplementary Digital Content [see Supplementary Materials, http://links.lww.com/AJG/D636]) (4). Patients ingested 25 g of lactose or fructose dissolved in 250 mL of sterile water. Testing for each carbohydrate was conducted on alternate days. Exhaled $H_2$ and $CH_4$ levels were measured at baseline (before the carbohydrate load) and every 30 minutes for 4 hours (lactose breath test) or 5 hours (fructose breath test). In both breath tests, an increase of ≥20 ppm in exhaled $H_2$ or ≥10

ppm in exhaled $CH_4$ from baseline was indicative of a positive test, signifying the presence of lactose/fructose malabsorption.

The aCPQ was administered to our patients during glucose, lactose, and fructose breath tests (15,16). At baseline and every end-alveolar breath sample collection, i.e., every 30 minutes (15 minutes for the glucose breath test), patients evaluated the intensity of 5 gastrointestinal symptoms (pain, nausea, bloating, flatulence, and diarrhea) using a Visual Analog Scale (VAS) ranging from 0 to 100. Lactose and fructose intolerances were defined as an increase of ≥20 mm in the VAS score from baseline in at least one of the 5 symptoms during the respective breath test, as this cutoff was previously used in another study by Klare et al (25). We considered patients to be carbohydrate intolerant if they met the aforementioned cutoff for lactose, fructose, or both.

The presence of gastrointestinal (GI) symptoms after ingesting glucose was also defined using the same cutoff and named "digestive intolerance to glucose." This digestive intolerance to glucose was not part of the definition of carbohydrate intolerance.

### Statistical analysis

Demographic and patient characteristics were first presented for the global study population. We then divided patients into groups based on the presence or absence of lactose intolerance and fructose intolerance and compared these groups (see Supplementary Table 1, http://links.lww.com/AJG/D636). As those groups were very similar, we decided to combine lactose intolerance and/or fructose intolerance into one group (i.e., carbohydrate intolerant group). Therefore, for the next analysis, we divided patients into 2 groups: carbohydrate intolerant and nonintolerant. The characteristics of carbohydrate intolerant patients were compared with those of nonintolerant patients. We also presented the patients according to the presence of maldigestion/malabsorption for each carbohydrate, to demonstrate the absence of difference in their profiles (see Supplementary Table 2, http://links.lww.com/AJG/D636).

To further understand the determinants of carbohydrate intolerance, we conducted a binary logistic regression using all factors independently associated with carbohydrate intolerance ($P < 0.1$) as covariates and carbohydrate intolerance as the dependent variable. Quality of life scores were excluded as it is a consequence of the symptoms. Multicollinearity was excluded before the regression analysis, defined as tolerance <0.1 (no multicollinearity was found).

Continuous variables are expressed as mean values ± SD, and categorical variables are expressed as number of patients and percentage. Independent sample T tests were used for quantitative and $\chi^2$ tests for qualitative analyses. A $P$ value below 0.05 was considered statistically significant. To have a better overview of the association between our variables, we used a correlogram. We pooled all our data: demographics (age, female sex, body mass index), breath test results (gas and symptoms), types of DGBI, and questionnaires (IBS severity, quality of life, anxiety, depression, somatization, insomnia, sleep quality). Regarding breath test results, we included the presence or absence of lactose maldigestion and fructose malabsorption (according to the European guidelines) but also the peak levels of exhaled $H_2$ and $CH_4$ for both tests (defined by the difference between baseline and the highest level of gas) and the peak symptoms (defined by the difference between baseline and the worst recorded symptom for each symptom) in each breath test (including glucose). Pearson correlation coefficients were computed between subjective and objective scales and plotted in a correlogram using pairwise complete observations. As the significance of a correlation is not the same as its strength (due to our large sample, some weak correlations may appear significant), and as we tested a large

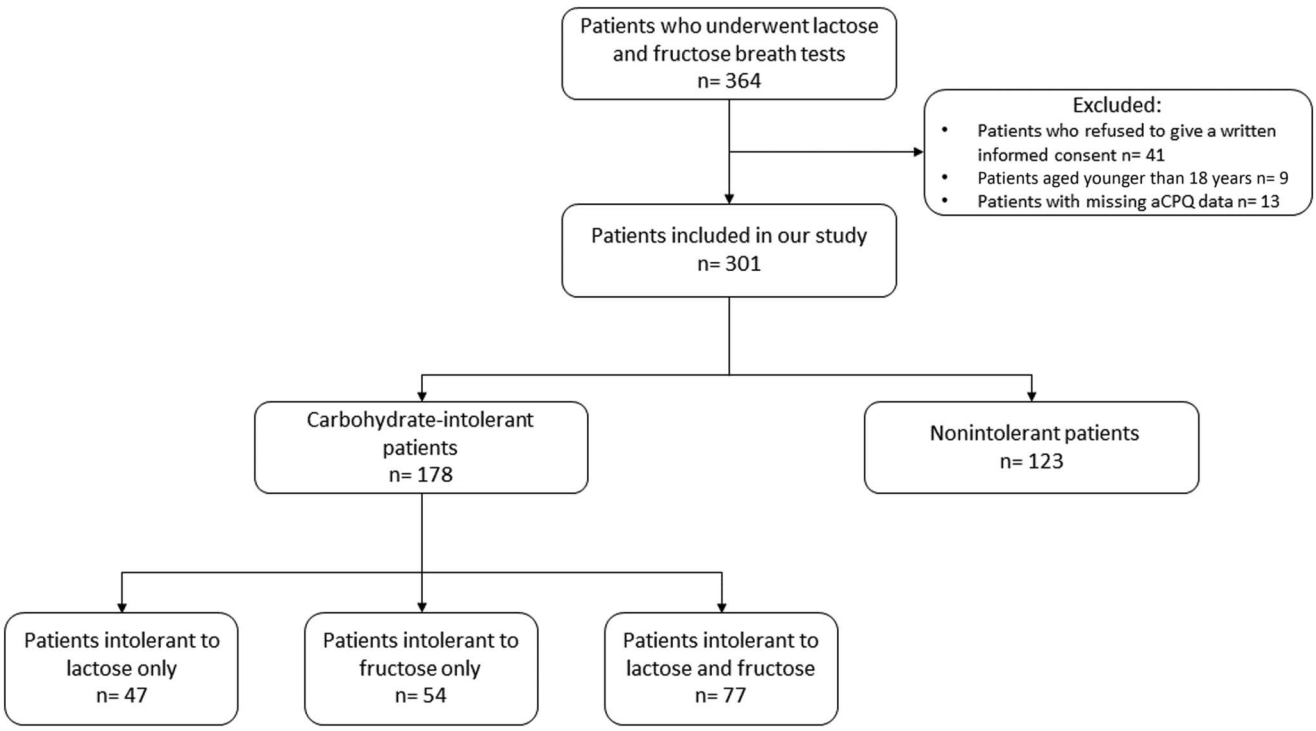


**Figure 1.** Patient flow chart. aCPQ, adult Carbohydrate Perception Questionnaire.

number of variables, we chose to show the correlation matrix along with Pearson correlation coefficients and *P* values in the Supplementary Digital Content (see Supplementary File, http://links.lww.com/AJG/D635).

We used IBM SPSS Statistics version 25 for comparison and logistic regression. R software (version 4.2.0; The R Foundation for Statistical Computing, Vienna, Austria) was used to create the correlogram.

## RESULTS

### Patients

In total, 364 patients had undergone lactose and fructose breath tests. Of these, 63 were excluded, leaving 301 patients in our study. Among them, 178 (59.1%) had carbohydrate intolerance (intolerant to lactose and/or fructose) (Figure 1). Although included patients had to test negative on glucose breath tests, 155 of 301 (51.5%) had GI symptoms above the aCPQ cutoff after glucose ingestion.

Patient demographics and characteristics are summarized in Table 1. Only 2 patients had diabetes (one with type 1 and one with type 2), and they did not meet the aCPQ cutoff after glucose ingestion. The 3 most frequent DGBI found in the 272 patients who have filled the Rome IV questionnaire were IBS (57%), functional bloating and abdominal distension (FBAD) (57%), and functional dyspepsia (FD) (45.6%). According to the questionnaires' results, patients had a moderate IBS-symptom severity, with few psychosocial comorbidities: without clinical anxiety and depression, but with mild insomnia severity, and medium somatic symptom severity levels (Table 1).

As for the breath test results, 133 patients had carbohydrate malabsorption (Table 1). When comparing patient characteristics between those with and without lactose and fructose malabsorption, we found very few differences (see Supplementary Table 2, http://links.lww.com/AJG/D636). Mainly patients with lactose maldigestion were more likely to have lactose intolerance and fructose malabsorption, and those with fructose malabsorption were more likely to have fructose intolerance and lactose maldigestion (see Supplementary Table 2, http://links.lww.com/AJG/D636). Interestingly, only 50 of 287 patients (17%) reported following a lactose-free diet, and they did not seem able to identify the need to follow such a diet based on the presence of maldigestion/intolerance (see Supplementary Table 3, http://links.lww.com/AJG/D636).

### Characteristics of patients with carbohydrate intolerance

Carbohydrate-intolerant patients were significantly more likely to be female ($P$ value $< 0.001$), to have 2 or more DGBI ($P$ value $= 0.001$), and to have lactose maldigestion and fructose malabsorption ($P$ value$< 0.001$ and 0.023) compared with nonintolerant patients (Table 2). Moreover, patients with carbohydrate intolerance had significantly higher IBS and somatic symptom severity levels, and lower quality of life ($P$ value$< 0.001$) compared with those who are nonintolerant (Table 2).

The aforementioned significant differences between carbohydrate-intolerant vs nonintolerant patients were similar when lactose and fructose intolerance were analyzed separately. We found that lactose intolerant patients had an association with lactose maldigestion and fructose intolerance, whereas fructose intolerant patients had an association with fructose malabsorption and lactose intolerance (see Supplementary Table 1, http://links.lww.com/AJG/D636). In addition, only fructose-intolerant

**Table 1. Patient characteristics**

| Characteristics | Value |
|---|---|
| Demographics (n = 301) | |
| Female | 211 (70.1) |
| Age (yr) | 43.7 ± 15.4 |
| BMI (kg/m$^2$) | 25.5 ± 5.8 |
| Type 1 diabetes | 1 (0.3) |
| Type 2 diabetes | 1 (0.3) |
| Rome IV criteria (n = 272) | |
| IBS | 155 (57.0) |
| IBS-C | 26 (16.8) |
| IBS-D | 57 (36.8) |
| IBS-M | 67 (43.2) |
| IBS-U | 5 (3.2) |
| FD | 124 (45.6) |
| EPS | 28 (22.6) |
| PDS | 49 (39.5) |
| EPS and PDS | 47 (37.9) |
| Functional bloating and abdominal distension | 155 (57.0) |
| Functional constipation | 39 (14.3) |
| Functional diarrhea | 69 (25.4) |
| Breath test results (n = 301) | |
| Lactose maldigestion only | 48 (16.0) |
| Fructose malabsorption only | 56 (18.6) |
| Lactose maldigestion and fructose malabsorption | 29 (9.6) |
| No malabsorption | 168 (55.8) |
| Lactose maldigestion based on the $H_2$ cutoff | 59 (76.6) |
| Lactose maldigestion based on the $CH_4$ cutoff | 6 (7.8) |
| Lactose maldigestion based on both cutoffs | 12 (15.6) |
| Fructose malabsorption based on the $H_2$ cutoff | 67 (78.8) |
| Fructose malabsorption based on the $CH_4$ cutoff | 8 (9.4) |
| Fructose malabsorption based on both cutoffs | 10 (11.8) |
| Questionnaire scores (n = 287) | |
| Quality of life (GIQLI) | 91.7 ± 20.2 |
| IBS Severity (IBS-SSS) | 223.9 ± 102.8 |
| Anxiety (HAD-A) | 7.8 ± 4.1 |
| Depression (HAD-D) | 5.4 ± 3.7 |
| Sleep quality (PSQI) | 7.8 ± 3.8 |
| Insomnia severity (ISI) | 10.4 ± 6.7 |
| Somatic symptom severity (PHQ-15) (n = 239) | 11.2 ± 5.4 |

Results are presented as mean ± SD, or number (percentage).
BMI, body mass index; EPS, epigastric pain syndrome; FD, functional dyspepsia; GIQLI, Gastrointestinal Quality of Life Index; HAD-A and D, Hospital Anxiety and Depression Scale (HAD-S); IBS, irritable bowel syndrome; IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; IBS-SSS, IBS Symptom Severity Scale; IBS-U, IBS unclassified; ISI, Insomnia Severity Index; PDS, postprandial distress syndrome; PHQ-15, Patient Health Questionnaire-15; PSQI, Pittsburgh Sleep Quality Index.

**Table 2. Comparison between patients with and without carbohydrate intolerance**

| Variable | Carbohydrate intolerance | Carbohydrate nonintolerance | *P* value |
|---|---|---|---|
| Demographics | n = 178 | n = 123 | |
| Female | 139 (78.1) | 72 (58.5) | **<0.001** |
| Age (yr) | 42.5 ± 15.8 | 45.4 ± 14.6 | 0.102 |
| BMI (kg/m$^2$) | 26.0 ± 6.2 | 24.9 ± 5.1 | 0.105 |
| No. of DGBI | n = 162 | n = 110 | |
| 1 | 69 (42.6) | 70 (63.6) | **0.001** |
| ≥2 | 93 (57.4) | 40 (36.4) | |
| Breath test results | n = 178 | n = 123 | |
| Lactose maldigestion | 59 (33.1) | 18 (14.6) | **<0.001** |
| Fructose malabsorption | 59 (33.1) | 26 (21.1) | **0.023** |
| Questionnaire scores | n = 169 | n = 118 | |
| Quality of life (GIQLI) | 87.5 ± 19.6 | 97.8 ± 19.6 | **<0.001** |
| IBS symptom severity (IBS-SSS) | 245.3 ± 99.3 | 193.2 ± 100.2 | **<0.001** |
| Anxiety (HAD-A) | 8.0 ± 4.0 | 7.6 ± 4.2 | 0.428 |
| Depression (HAD-D) | 5.7 ± 3.8 | 4.9 ± 3.5 | 0.071 |
| Sleep quality (PSQI) | 8.0 ± 3.9 | 7.4 ± 3.7 | 0.190 |
| Insomnia severity (ISI) | 10.9 ± 6.9 | 9.7 ± 6.3 | 0.126 |
| | n = 137 | n = 102 | |
| Somatic symptom severity (PHQ-15) | 12.4 ± 5.3 | 9.7 ± 5.0 | **<0.001** |

Results are presented as mean ± SD, or number (percentage). Bold values indicate statistically significant differences ($p<0.05$). Carbohydrate intolerant patients have lactose and/or fructose intolerance.
BMI, body mass index; DGBI, disorders of gut-brain interaction; GIQLI, Gastrointestinal Quality of Life Index; HAD-A and D, Hospital Anxiety and Depression Scale (HAD-S); IBS-SSS, IBS Symptom Severity Scale; ISI, Insomnia Severity Index; PHQ-15, Patient Health Questionnaire-15; PSQI, Pittsburgh Sleep Quality Index.

patients had significantly higher anxiety, depression, and insomnia severity scores, and worse sleep quality compared with nonfructose-intolerant patients (see Supplementary Table 1, http://links.lww.com/AJG/D636). These differences were no longer significant after the combination of patients into the positive carbohydrate intolerance group (Table 2).

For qualitative visualization, symptom and exhaled gas level evolution for lactose intolerant (I+) vs lactose nonintolerant (I−) and fructose intolerant (I+) vs fructose nonintolerant (I−) patients were, respectively, represented in Figures 2 and 3. Both fructose and lactose I+ patients had the highest VAS scores for pain and bloating among the 5 symptoms (Figures 2a,c and 3a,c). These peak pain and bloating VAS scores were reached, respectively, around 90 and 120 minutes after lactose ingestion and around 90 minutes after fructose ingestion. Lactose I+ patients had higher exhaled $H_2$ levels than those who are lactose I−, with peak levels reached around 150 minutes after the lactose load (Figure 2f), whereas in fructose I+ patients, exhaled $H_2$ peak levels were lower than in lactose I+ and were reached around 120 minutes after fructose ingestion (Figure 3f). $CH_4$ levels were approximately the same in both lactose and fructose, I+ and I− groups (Figures 2g and 3g).

As for the binary logistic regression analysis, the model contained 7 independent variables (sex, number of DGBI, lactose maldigestion, fructose malabsorption, IBS-SSS, depression, and somatic symptom severity) and was statistically significant (*P* value < 0.001) (Table 3). We found that somatic symptom severity, lactose maldigestion, but not fructose malabsorption, were independently associated with carbohydrate intolerance (Nagelkerke R Square = 0.206).

### Correlation between carbohydrate-induced symptoms and other variables

Correlations can be visualized in the correlogram in Figure 4, and Pearson correlation coefficients and the *P* values are presented in the Supplementary Digital Content (see Supplementary File, http://links.lww.com/AJG/D635).

We found that pain ($r = 0.22$, 0.10–0.34), bloating ($r = 0.30$, 0.18–0.41), and flatulence ($r = 0.34$, 0.21–0.46) symptoms after lactose ingestion were weakly positively correlated with lactose maldigestion. Nausea ($r = 0.17$, 0.04–0.29) and diarrhea ($r = 0.20$, 0.07–0.32) symptoms after lactose ingestion had an even weaker positive correlation with lactose maldigestion. Moreover, after lactose ingestion, pain ($r = 0.37$; 0.19–0.52) and bloating ($r = 0.39$, 0.22–0.53) symptoms were weakly positively correlated, and flatulence symptoms were moderately positively correlated ($r = 0.46$, 0.28–0.61) with lactose $H_2$ peak levels. Same as for their correlation with lactose maldigestion, nausea (0.16, 0.01–0.30) and diarrhea (0.25, 0.10–0.39) symptoms after lactose ingestion were weakly positively correlated with lactose $H_2$ peak levels, whereas fructose intolerance symptoms had negligible positive correlations with fructose malabsorption (Figure 4, see Supplementary File, http://links.lww.com/AJG/D635).

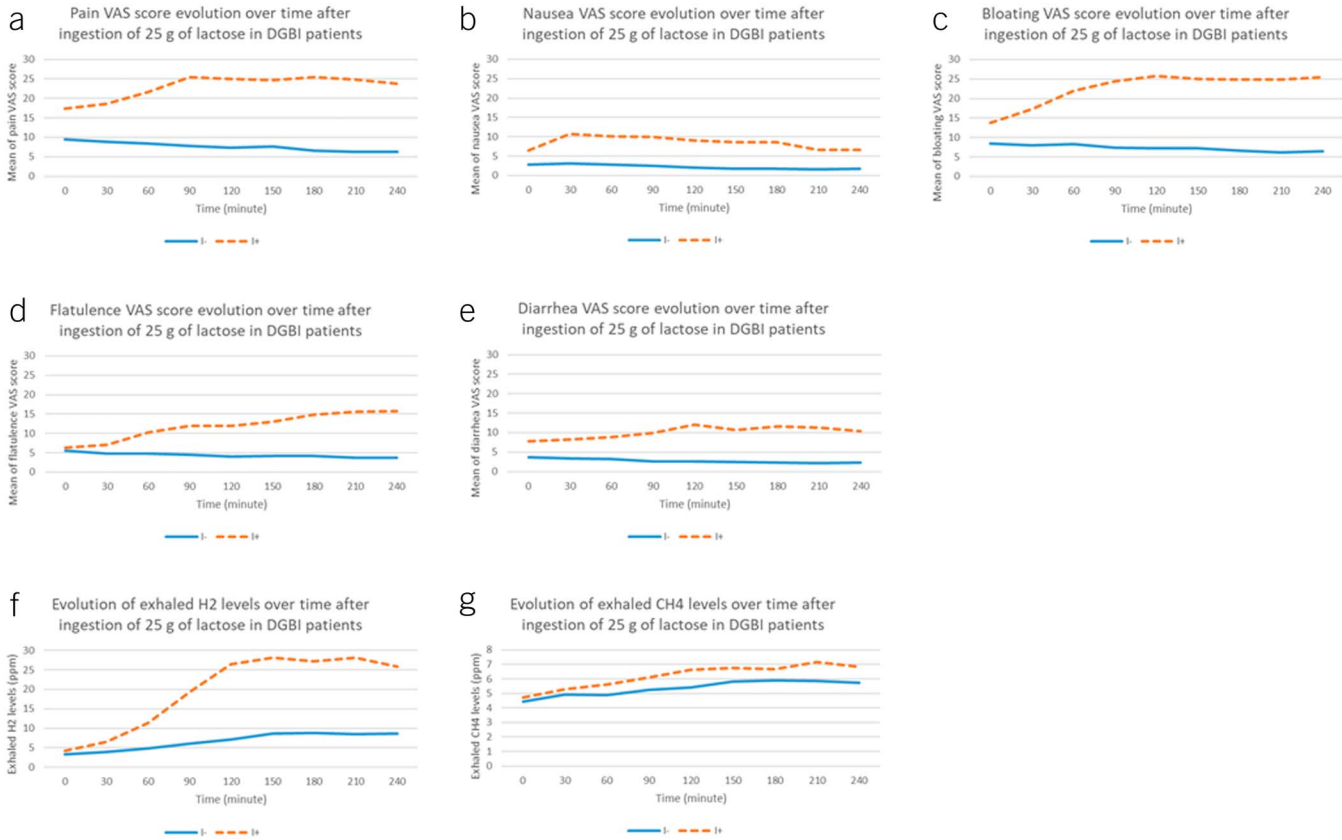


**Figure 2.** Evolution of the 5 adult Carbohydrate Perception Questionnaire (aCPQ) Visual Analog Scale (VAS) symptom scores (**a**: pain, **b**: nausea, **c**: bloating, **d**: flatulence, **e**: diarrhea) and exhaled H2 and CH4 levels (**f** and **g**) over time after a load of 25 g of lactose in patients with DGBI. Patients without lactose intolerance (I−, solid line; n = 177), patients with lactose intolerance (I+, dashed line; n = 124). Mean values are shown. DGBI, disorders of gut-brain interaction.

Each intolerance symptom for both lactose and fructose was slightly positively correlated to the symptoms after glucose intake (control without malabsorption) and to the other carbohydrate-induced symptoms. Glucose symptoms and carbohydrate intolerance were also positively correlated to IBS-SSS, somatic symptom severity, and, to a lesser extent, anxiety and depression symptoms, sleep quality, and insomnia severity levels (with a stronger correlation in glucose symptoms than lactose and fructose intolerance symptoms). Symptoms of lactose and fructose intolerance were negatively correlated with quality of life, as were symptoms after glucose ingestion.

Furthermore, the type of DGBI was not correlated with carbohydrate intolerance. Even pain intolerance (pain in relation with carbohydrate ingestion) was not correlated with IBS, only lactose bloating seemed weakly correlated with IBS and FD. FD was correlated with symptoms after glucose intake. Symptoms after glucose intake were also correlated with IBS-SSS and somatic symptoms.

Finally, IBS, FD, and FBAD were positively correlated with IBS-SSS and somatic symptom severity, and weakly with anxiety, depression, insomnia, and sleep disorders, and negatively correlated to quality of life (with FBAD having weaker correlations).

## DISCUSSION

In this study, we aimed to evaluate the prevalence of carbohydrate (lactose and fructose) intolerance in patients with DGBI and to characterize the carbohydrate-intolerant subgroup. A large proportion of patients with DGBI had carbohydrate intolerance (59%). They were found to be female with more than 2 DGBI overlapping and to have more IBS and somatic symptom severity and a lower quality of life compared with nonintolerant patients. Lactose maldigestion and fructose malabsorption were more frequently present in patients with carbohydrate intolerance (in 33% of them) compared with those who are nonintolerant. Somatic symptom severity and lactose maldigestion were also independently associated with carbohydrate intolerance.

Intolerance to both lactose and fructose was common in the carbohydrate-intolerant subgroup (43%). When we analyzed lactose and fructose intolerance separately, we found that carbohydrate maldigestion/malabsorption was associated with the intolerance of the same carbohydrate and that patients intolerant to one carbohydrate were also more likely to be intolerant to the other. However, the binary logistic regression analysis showed that only lactose maldigestion, and not fructose malabsorption, was independently associated with carbohydrate intolerance. This result was in line with those of the correlogram, which showed positive correlations between lactose maldigestion and lactose-induced symptoms, but weaker correlations between fructose malabsorption and fructose-induced symptoms. These findings suggest that lactose maldigestion is involved in lactose intolerance, whereas fructose malabsorption does not seem to be involved in fructose intolerance. In fact, it had already been found that fructose and lactose intolerance can occur without lactose maldigestion or fructose malabsorption (26,27). This indicates

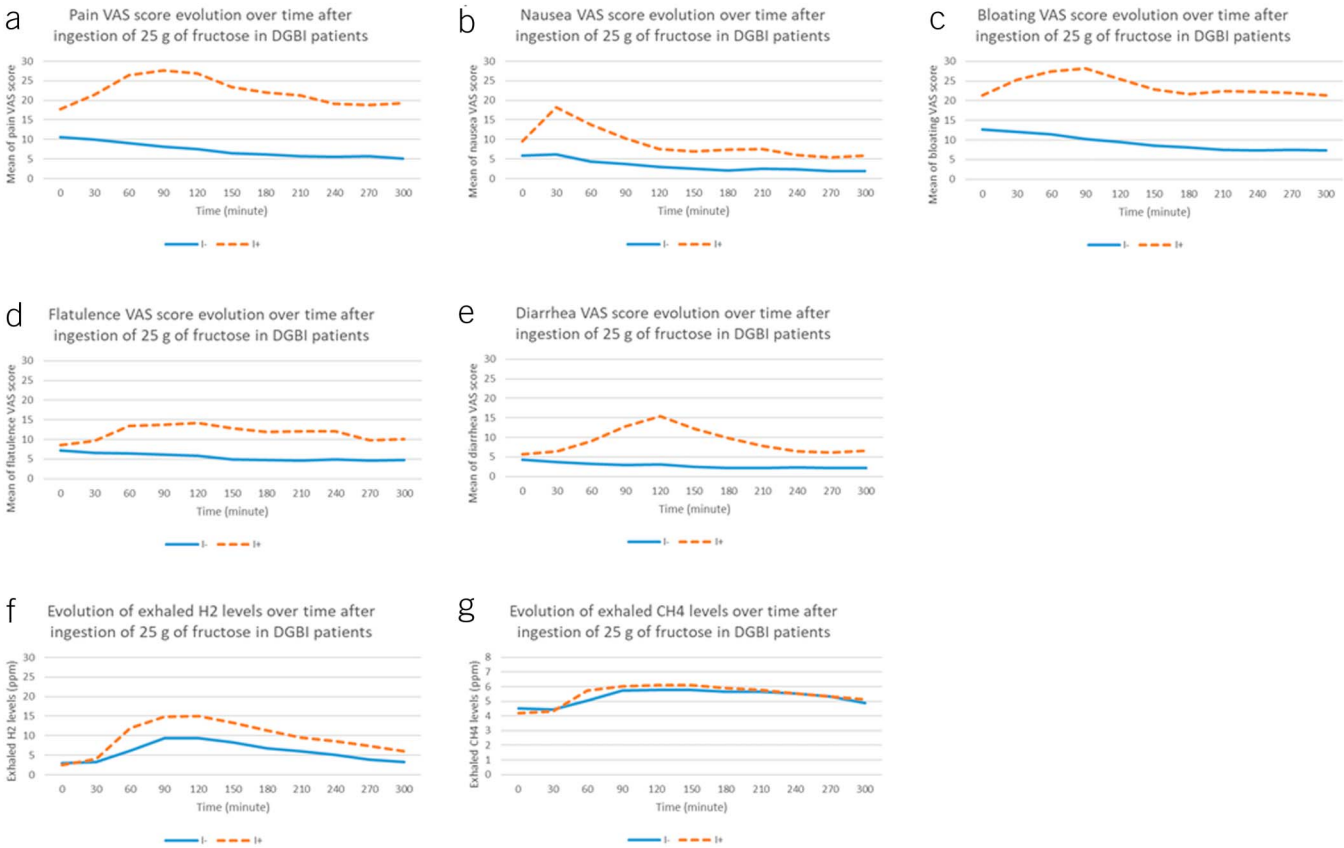


**Figure 3.** Evolution of the 5 adult Carbohydrate Perception Questionnaire (aCPQ) Visual Analog Scale (VAS) symptom scores (**a**: pain, **b**: nausea, **c**: bloating, **d**: flatulence, **e**: diarrhea), and exhaled H2 and CH4 levels (**f** and **g**) over time after a load of 25 g of fructose in patients with DGBI. Patients without fructose intolerance (I−, solid line; n = 170), patients with fructose intolerance (I+, dashed line; n = 131). Mean values are shown. DGBI, disorders of gut-brain interaction.

that mechanisms other than malabsorption may be implicated or that the tests used are not very reliable. More than half of our included patients (51.5%) had GI symptoms above the aCPQ cutoff after glucose ingestion. This percentage is higher than in a previous study, where 21% of patients with IBS reported symptoms after ingesting glucose, but could be explained by the difference in glucose intake (75 g in our study vs 40 g) (8). The presence of GI symptoms after a glucose load is known and might implicate several mechanisms, such as osmolarity, gastrointestinal motility, and presence of plasmatic hormones (28,29). This reinforces the hypothesis that mechanisms other than malabsorption are implicated in intolerance. Intestinal microbiota

**Table 3. Binary logistic regression analysis of the dependent variable: carbohydrate intolerance**

| | Carbohydrate intolerance (n = 226) Nagelkerke R Square = 0.206 | | | | |
|---|---|---|---|---|---|
| **Independent variable** | **B** | **SE** | ***P* value** | **OR** | **95% CI** |
| Female | 0.287 | 0.332 | 0.387 | 1.333 | 0.696–2.552 |
| No. of DGBI | 0.428 | 0.324 | 0.187 | 1.534 | 0.813–2.895 |
| Lactose maldigestion | 1.160 | 0.360 | **0.001** | 3.189 | 1.576–6.452 |
| Fructose malabsorption | 0.151 | 0.343 | 0.660 | 1.163 | 0.594–2.279 |
| IBS symptom severity (IBS-SSS) | 0.003 | 0.002 | 0.157 | 1.003 | 0.999–1.006 |
| Depression (HAD-D) | −0.055 | 0.47 | 0.246 | 0.947 | 0.863–1.038 |
| Somatic symptom severity (PHQ-15) | 0.089 | 0.040 | **0.025** | 1.093 | 1.011–1.182 |
| Constant | −1.682 | 0.466 | <**0.001** | 0.186 | |

Bold values indicate statistically significant associations (p<0.05) in the logistic regression model. BMI, body mass index; CI, confidence interval; DGBI, disorders of gut-brain interaction; HAD-D, Hospital Anxiety and Depression Scale (HAD-S); IBS-SSS, IBS Symptom Severity Scale; OR, odds ratio; PHQ-15, Patient Health Questionnaire-15; SE, standard error; .

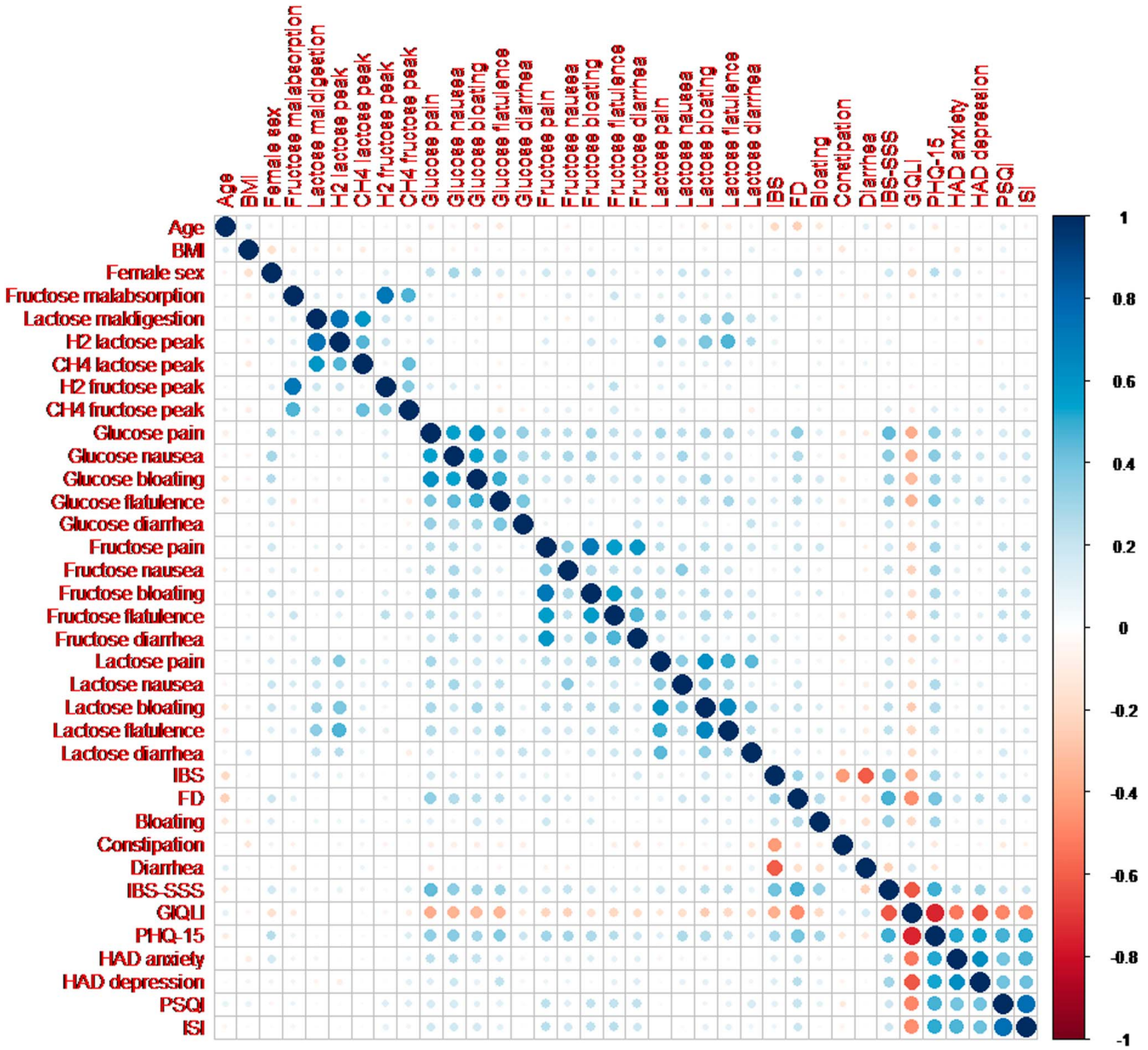


**Figure 4.** Correlogram demonstrating correlations (Pearson *r*) between subjective and objective variables. Blue shades represent positive correlations, and red shades represent negative correlations. The shade and size of the circles are proportional to the correlation coefficients. FD, functional dyspepsia; GIQLI, Gastrointestinal Quality of Life Index; HAD-A and D, Hospital Anxiety and Depression Scale (HAD-S); IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Scale; ISI, Insomnia Severity Index; PHQ-15, Patient Health Questionnaire-15; PSQI, Pittsburgh Sleep Quality Index.

alterations, colonic motor response, and colonic distension were found to be possible mechanisms behind the occurrence of symptoms after carbohydrate ingestion (30–32). In addition, the ingestion of small molecular carbohydrates such as fructose, which are osmotically active, can lead to fluid accumulation in the small intestine, causing small bowel distension and abdominal symptoms (32,33). Research suggests that visceral hypersensitivity, rather than malabsorption or excessive gas production, may play a role in fructose-induced symptoms (7,8). Another recent study identified a new peripheral mechanism for food-induced abdominal pain, involving an IgE-dependent and mast-cell-dependent reaction limited to the intestine and inducing visceral pain (34). These findings suggest a local allergy-like reaction to food because of a loss of tolerance to dietary antigens after a GI infection (34). Those mechanisms can be investigated with confocal laser endomicroscopy. IBS patients with suspected food intolerance were found to have immediate increased intervillous spaces and intraepithelial lymphocytes in the intestinal mucosa after exposure to food antigens (35). So, this local allergy-like reaction to food may also be implicated in the mechanisms behind food intolerance in patients with DGBI.

Carbohydrate-reduced diets have been found effective in reducing symptoms in patients, regardless of the presence of maldigestion/malabsorption (13,36–38). This suggests that even patients without malabsorption might benefit from diets low in lactose and/or fructose. In a recent study where they used the aCPQ to diagnose carbohydrate intolerance, they found that 30% of patients with lactose intolerance and 22% with

fructose intolerance did not have carbohydrate maldigestion/malabsorption, yet experienced symptom improvement after the suggested treatment (a low-carbohydrate diet and optional dietary supplements) (25). However, to date, no double-blind placebo-controlled study has been conducted to evaluate the effect of low-carbohydrate diets based on the presence of intolerance. Such a study could help confirm the importance of intolerance in identifying patients who can respond to the diet, or it might indicate that other treatments targeting potential mechanisms, such as visceral hypersensitivity, should also be considered.

Somatic symptom severity was significantly higher in patients with carbohydrate intolerance, and this difference was clinically relevant. Indeed, patients with carbohydrate intolerance experienced medium somatic symptoms whereas patients without carbohydrate intolerance experienced low somatic symptoms (24). Alongside lactose maldigestion, somatic symptom severity was also independently associated with carbohydrate intolerance, as found in our binary logistic regression analysis. Moreover, our correlogram also suggests a correlation between somatic symptom severity and carbohydrate-induced symptoms. This association between somatic symptom severity and carbohydrate intolerance aligns with another study that found that symptoms of lactose intolerance were not related to lactose maldigestion but were significantly associated with altered somatic symptom severity scores (27). This result could be explained by a generalized tendency to report pain as previously suggested in a study demonstrating that somatization was common in patients with IBS and was inversely correlated with pain thresholds (39). We found that carbohydrate intolerance patients were more likely to have 2 or more DGBI than nonintolerant patients. Studies have found that somatic symptoms were significantly associated with having any DGBI, and somatic severity levels increased as the number of overlapping DGBI regions increased (40–42). Probably, somatic symptom severity was more strongly associated with carbohydrate intolerance than the number of DGBI, explaining the fact that only somatic symptom severity was independently associated at the end.

Our study significantly contributes to the understanding of carbohydrate intolerance in a robust cohort of patients with DGBI. We assessed lactose maldigestion and fructose malabsorption according to the European guidelines on hydrogen and methane breath tests (4). Unlike previous studies that used various nonvalidated tools, we used the aCPQ, a validated questionnaire specific for carbohydrate intolerance diagnosis (15,16). However, it is important to acknowledge some limitations. First, our study was monocentric. Second, the potential influence of a nocebo effect should be considered, as de Graaf et al found it had an important role in symptom occurrence in noncoeliac gluten sensitivity, it might also have a role in the onset or aggravation of symptoms after carbohydrate load (43). We also have not performed a placebo breath test, as breath tests were conducted in our clinical routine, and the placebo might be difficult to find. Third, breath tests involve ingesting a single carbohydrate (in a drink), whereas in real life, carbohydrates are consumed in more complex meals at different doses than those used in breath tests (44,45). Thus, carbohydrate consumption during breath tests might not be fully representative of real-world scenarios. In addition, lactose and fructose breath tests were not performed blindly. However, a study demonstrated the repeatability for intolerance status in fructose breath tests, and the authors concluded that the fructose breath test can be used unblinded in functional gastrointestinal disorders (46). Finally, the cutoff used for diagnosing intolerance has been previously used, but it requires further validation (25). One way to validate this cutoff is by testing its relevance in the evaluation of exclusion diets. This would help determine if the cutoff is useful for identifying individuals who benefit from such diets.

In conclusion, our study demonstrated that a substantial proportion of patients with DGBI has carbohydrate intolerance. This subgroup reported more severe IBS symptoms and somatic symptoms, and a reduced quality of life. Our model suggested that only lactose maldigestion and somatic symptom levels were independently associated with the presence of carbohydrate intolerance and that other mechanisms might be involved. Our findings highlight the importance of assessing carbohydrate intolerance to develop tailored and improved management strategies in DGBI. Future research should define the underlying mechanisms and identify which treatments might benefit these patients.

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## CONFLICTS OF INTEREST

**Guarantor of the article:** Chloé Melchior, MD, PhD.

**Specific author contributions:** C.M. and G.G.: planned the study. C.D., A.M.L., C.M. and G.G.: conducted the study. H.M.M.: collected the study. H.M.M. and A.G.: interpreted data, and all authors drafted the manuscript. All authors have approved the final draft submitted.

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## Study Highlights

### WHAT IS KNOWN

- ✓ Food-related symptoms are common in disorders of gut-brain interaction (DGBI).
- ✓ Research on carbohydrate intolerance in DGBI is very heterogeneous.

### WHAT IS NEW HERE

- ✓ Carbohydrate intolerance affects a large proportion of patients with DGBI.
- ✓ Carbohydrate-intolerant patients have a lower quality of life and higher symptom severity.
- ✓ Somatic symptom severity and lactose maldigestion are independently associated with carbohydrate intolerance.

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