Neurogastroenterology & Motility

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Neurogastroenterology & Motility NGM

ORIGINAL ARTICLE OPEN ACCESS

Beyond Malabsorption: The Need for Symptom-Based Assessment in Suspected Lactose Intolerance. Lessons From a Test-Specific Symptom Assessment

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Received: 29 June 2025 | **Revised:** 1 August 2025 | **Accepted:** 8 September 2025

Funding: The authors received no specific funding for this work.

Keywords: adult carbohydrate perception questionnaire (aCPQ) | breath test | lactose intolerance | lactose malabsorption | symptom burden

ABSTRACT

Background: Lactose malabsorption is commonly assumed to cause gastrointestinal discomfort, but symptoms often persist despite lactose restriction or enzyme supplementation.

Objective: This study aimed to assess symptoms following lactose ingestion, its relationship with malabsorption, and its association with fructose sensitivity and disorders of the gut-brain interactions (DGBIs).

Design: In 753 consecutive patients with DGBIs, we performed hydrogen breath tests and used the validated adult Carbohydrate Perception Questionnaire (aCPQ) to assess lactose-induced symptoms. Lactose malabsorption (LM+) was defined as a hydrogen increase of >20 ppm. Lactose induced burdensome symptoms (LS+) were defined by a visual analogue scale (VAS) increase of >20 mm. Fructose sensitivity was assessed in 547 patients using the same protocol.

Results: LM+ was observed in 40.9% of patients, while 55.4% reported LS+. Interestingly, 45.3% of symptomatic patients had no lactose malabsorption (LM−) and 26.0% of malabsorbers had no symptoms (LS−). LS+ were significantly more likely to exhibit fructose sensitivity (45.2% vs. 24.2% in LS−, $p<0.001$). DGBIs were similarly distributed in LS+ patients with and without malabsorption. Functional dyspepsia and irritable bowel syndrome were significantly more frequent in LS+, irrespective of whether lactose was malabsorbed or not, than in those without lactose-induced symptoms (with or without malabsorption).

Conclusion: Lactose malabsorption alone is an inadequate predictor of the occurrence of symptoms, emphasizing the need for comprehensive symptom assessment beyond breath test results. This has important implications for the selection of appropriate therapies. The association between lactose and fructose sensitivity suggests a role for visceral hypersensitivity and overlapping mechanisms in symptom development.

Abbreviations: aCPQ, adult carbohydrate perception questionnaire; DGBI, disorder of gut-brain interaction; H_2, hydrogen; H_2BT, hydrogen breath test; IBS, irritable bowel syndrome; LM+, lactose malabsorption; LM−, no lactose malabsorption or lactose absorption; LS+, lactose induced symptoms; LS−, no lactose induced symptoms.

Summary

- Malabsorption documented by breath testing does not reliably predict symptom occurrence following lactose ingestion.
- A large proportion of patients without malabsorption experience significant symptoms.
- Symptoms after lactose ingestion are associated with fructose sensitivity and functional GI disorders.
- Validated, test-specific symptom assessment is needed to effectively assess symptom burden after lactose ingestion and identify patients who might benefit from treatment.

1 | Introduction

Primary lactose malabsorption is a widespread condition, affecting millions of individuals globally, with varying prevalence depending on ethnic background [1, 2]. The condition is caused by a deficiency of the enzyme lactase. In the absence of this enzyme, lactose, a disaccharide present in dairy products, remains undigested and undergoes fermentation in the colon [3]. For decades, lactose malabsorption was assumed to be the primary cause of the abdominal symptoms of lactose intolerance, leading to the two terms being used interchangeably [4]. More recently, however, it became evident that lactose malabsorption and the development of symptoms may not necessarily be causally related. Consequently, the recently published European guideline makes a clear distinction between these two entities [5]. Lactose malabsorption refers to the incomplete absorption of lactose in the small intestine, resulting in its colonic fermentation by bacteria into hydrogen, methane, and short-chain fatty acids. In contrast, lactose intolerance refers to the clinical manifestation of gastrointestinal symptoms such as bloating, abdominal distension, nausea, abdominal cramps, and diarrhea following ingestion of lactose [3, 4, 6]. Notably, while lactose malabsorption is frequently associated with lactose intolerance, the two terms are not synonymous, as many individuals with lactose malabsorption remain asymptomatic after a lactose challenge, and the severity of symptoms can vary greatly between individuals [7–9].

The predominant diagnostic approach to evaluate the potential role of lactose in causing bloating, abdominal distension, nausea, abdominal cramps, and diarrhea has been based on the identification of malabsorption, typically by documenting an increase in breath hydrogen levels following lactose ingestion [10, 11]. However, as the relationship between lactose malabsorption and the development of these symptoms remains unclear and is a complex area of research, patient-reported outcomes, such as symptom burden assessment, have gained increasing attention [5]. The adult Carbohydrate Perception Questionnaire (aCPQ) is a validated test-specific instrument designed to assess the symptom burden after carbohydrate ingestion, including lactose, and provides a symptom assessment that complements the traditional breath test [12]. This tool allows for a more nuanced understanding of the symptomatology associated with lactose ingestion, regardless of malabsorption status.

The objective of this study was to assess the relationship between lactose malabsorption, as determined by hydrogen breath testing (H2BT), and the symptoms following lactose ingestion, the overlap between lactose and fructose sensitivity and malabsorption, and to relate breath test results to disorders of gut-brain interaction. This approach was chosen to address several unresolved questions regarding the clinical significance of carbohydrate malabsorption in patients with gastrointestinal symptoms suggestive of carbohydrate-induced symptoms after the exclusion of organic gastrointestinal disorders. It allowed us to determine the extent to which lactose malabsorption is associated with lactose-induced symptoms, the extent to which lactose symptom burden exists independently of malabsorption, and the extent to which other clinical factors suggestive of visceral hypersensitivity may influence lactose sensitivity. In doing so, our data will provide a more comprehensive understanding of the mechanisms behind lactose-related symptoms and may lead to more effective diagnostic and therapeutic strategies for the management of lactose-induced symptoms.

2 | Methods

A prospective observational study was conducted on 753 consecutive patients who were referred for lactose breath testing at the gastrointestinal outpatient units of the two involved university hospitals (Vienna and Graz, Austria). The lactose breath test was performed in patients whose medical history suggested to the referring physicians a link between abdominal symptoms and lactose consumption, after organic causes and small intestinal bacterial overgrowth (glucose-H_2 breath test) had been ruled out [4]. This study was approved by the Ethics Committees of the Medical Universities of Vienna (EK no. 2049/20217 and 1420/2024) and Graz (29-467 ex 16/17 and 34-321 ex 21/22); the trial was performed from 3/2017 to 5/2023.

Each patient underwent a standard H_2 breath test after drinking a suspension of 50 g of lactose in 200 mL of water [5]. Patients were routinely instructed to abstain from food for 12 h before the test and to drink only water during this period. In addition, patients were instructed to avoid certain foods 24 h before the nothing-per-mouth request, to abstain from smoking and passive smoking for at least 1 h before and at any time during the test. Sleeping during the test was also prohibited to avoid suppression of gastrointestinal motility. The breath test was scheduled so that antibiotic treatment had been stopped at least 7 days before the test. End-expiratory breath samples were collected and analyzed for H_2 using an electrochemical hydrogen detector (Vienna: GMI- H_2-Analyzer; Stimotron medical devices, Hamburg, Germany; Graz: GastroCH4eck Gastrolyzer, www.bedfont.com). Both devices have a resolution of 1 ppm, an accuracy of ±5% to 10% of the reading, and a repeatability of < 5% difference on consecutive readings, as specified in their respective manuals. These features ensure reliable and consistent measurements across instruments [13]. Breath samples were analyzed before lactose was ingested (baseline) and 30, 60, 120, and 180 min after lactose ingestion. Baseline H_2 concentration ≤ 20 ppm was required before test initiation. Lactose malabsorption (LM+) was defined by an increase in end-expiratory

hydrogen levels of more than 20 ppm above baseline. Patients whose hydrogen increases did not exceed 20 ppm were classified as non-malabsorbers (LM−).

Gastrointestinal symptoms were evaluated using the aCPQ, a validated, test-specific tool comprising five 100 mm visual analog scales (VAS) which are used to assess the extent to which patients are burdened by abdominal pain, bloating, nausea, flatulence, and diarrhea [12]. Patients were required to complete the aCPQ before lactose ingestion (baseline) and subsequently concurrently with the collection of breath samples. A burdensome symptom response (LS+) was defined as an increase of more than 20 mm on any VAS scale from baseline. Patients without such an increase were classified as not symptomatic (LS−). The severity of each symptom was recorded as the maximum increase over baseline, with the highest possible score being 100 mm for each symptom. The total symptom burden was calculated as the sum of individual symptom burdens, yielding a maximum possible score of 500 mm.

The patients were divided into four categories based on the presence or absence of malabsorption and the presence or absence of burdensome symptoms:

- symptomatic lactose malabsorbers: L(S+M+),
- asymptomatic malabsorbers: L(S−M+),
- symptomatic non-malabsorbers: L(S+M−),
- asymptomatic non-malabsorbers: L(S−M−).

In 547 patients who received the lactose challenge, an additional fructose challenge (25 g) was performed. The fructose breath test was performed on patients referred by their referring physicians based on their medical history. The criteria for fructose symptom response and fructose malabsorption were determined in the same manner as for the lactose challenge, using the aCPQ and breath testing. There was an interval of at least one week between tests, and the same device was used for the second test on the same patient.

Rome IV criteria were used for the diagnosis of disorders of the gut-brain interactions. In patients with irritable bowel syndrome, the severity of clinical symptoms was assessed using the IBS-SSS scale [14].

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY). Continuous variables were analyzed using the Student's *t*-test, while categorical variables were analyzed using the chi-square test, ANOVA tests were utilized for multiple comparisons. A multivariate binary logistic regression analysis was performed to identify independent predictors of lactose-induced symptom response (LS+). The dependent variable was the presence of burdensome symptoms following a standardized lactose challenge (LS+). Covariates included sex, age, lactose malabsorption (LM+), fructose malabsorption and sensitivity, and the presence of functional gastrointestinal disorders (irritable bowel syndrome, functional diarrhea, functional constipation). Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Model fit was assessed using the Hosmer–Lemeshow test and classification tables. A p-value of <0.05 was considered statistically significant. Data are presented as mean ± standard deviation (SD).

3 | Results

Demographic characteristics of the 753 patients are shown in Table S1 and Figure S1. Three hundred eight of these patients (40.9%) were LM+, while 445 patients (59.1%) were LM− (Figure 1). Four hundred seventeen patients (55.4%) were LS+ and 336 patients (44.6%) were LS− (Figure 1). Among the 308 lactose-malabsorbers, 80 patients (26.0%) did not report burdensome symptoms L(S−M+), and among the 445 patients who did not malabsorb lactose, 189 patients (45.3%) experienced burdensome symptoms (Figure 1). From the perspective of those with symptoms, 189 patients (45.3%) had no malabsorption, while 80 patients (23.8%) with no burdensome symptoms had malabsorption (Figure 1).

3.1 | Lactose Sensitivity and Lactose Malabsorption

In the LS+ group, malabsorbers had a significantly higher total symptom burden compared to non-malabsorbers (Table 1). In the L(S+M+)-group the following symptoms were significantly more burdensome as compared to the (L(S+M−)-group: abdominal pain (32.0 ± 26.1 mm VAS) vs. 16.4 ± 18.6 mm VAS; $p<0.001$), bloating (32.0 ± 25.9 mm VAS vs. 19.9 ± 19.6 mm VAS; $p<0.01$), flatulence (34.4 ± 27.5 mmVAS vs. 16.4 ± 18.8 mm VAS; $p<0.001$), and diarrhea (33.2 ± 35.6 mm VAS vs. 9.4 ± 19.8 mm VAS; $p<0.001$). The percentage of LS+ patients affected by each of the above symptoms was also significantly higher in malabsorbers than in non-malabsorbers. Notably, there was no significant difference between the L(S+M+) and the L(S+M−) groups in the percentage of patients reporting burdensome nausea (16.9 ± 20.8 mm VAS vs. 18.2 ± 21.9 mm VAS; $p=0.5$). However, the symptom burden with nausea in both groups was

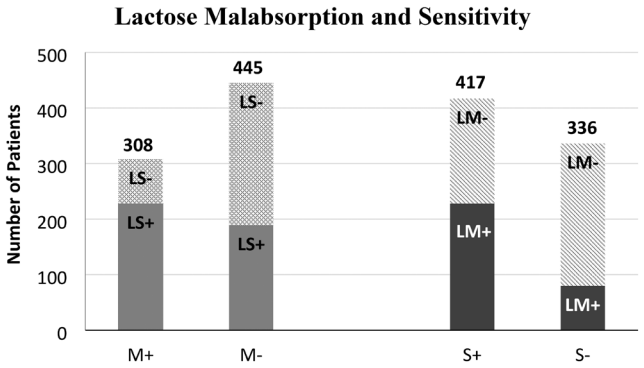

FIGURE 1 | Results of the lactose sensitivity/H_2-breath test in 753 patients with disorders of the gut-brain interactions. LM+, lactose malabsorbers; LM−, lactose non-malabsorbers; LS+, patients with lactose induced symptoms; LS−, patients without lactose induced symptoms; M, malabsorption; S, symptoms. 26.0% of LM+ (80 patients) had no burdensome symptoms after lactose challenge; 45.3% of LM− (189 pat.) had burdensome symptoms after lactose challenge; 45.3% of LS+ (189 pat.) had no lactose malabsorption after lactose challenge; 23.8% of LS− (80 pat.) had lactose malabsorption after lactose challenge.

significantly higher than in the two groups that did not exhibit any burdensome symptoms after lactose ingestion (L(S−M+) and L(S−M−); all $p < 0.001$, data not shown in Table 1).

Lactose malabsorption (LM+) predicted symptom presence (LS+) with a test sensitivity of 54.6%, specificity of 76.2%, PPV of 74.0%, and NPV of 57.5%. The positive likelihood ratio was 2.29, and the negative likelihood ratio was 0.60.

3.2 | Fructose Sensitivity and Lactose Sensitivity/Malabsorption

The demographic characteristics and results of the lactose sensitivity/H_2-breath test in patients who had breath tests with lactose only compared with patients who had breath tests with lactose and fructose are shown in Table S2. The prevalence of fructose sensitivity was 38.4% in LM+ patients compared to 34.2% in LM− patients (NS) (Table 2). However, fructose sensitivity was significantly more prevalent in LS+ than in LS− (45.2% vs. 24.2%; $p < 0.001$). This association was independent of lactose malabsorption status. Specifically, 42.8% of L(S+M+) were fructose sensitive, compared to 48.2% of L(S+M−) (NS). In contrast, LS− exhibited a low prevalence of fructose sensitivity, irrespective of malabsorption status (24.1% in L(S−M−) and 24.5% in L(S−M+); NS).

Fructose malabsorption was found in 38.4% of LM+ and 25.0% of LM− ($p < 0.01$). This association was independent of lactose-related symptoms. Specifically, 34.0% of L(S−M+) were fructose malabsorbers, compared to 39.8% of L(S+M+) (NS). 31.7% of LS+ compared to 28.7% of LS− were fructose malabsorbers (NS) (Table 2).

3.3 | Disorder of Gut-Brain Interaction

Table 3 shows that the IBS-SSS scores in patients with IBS were not significantly different between the four different groups

TABLE 1 | Group mean ± standard deviation of individual and total symptom burden in relation to the lactose sensitivity/H_2-breath test results.

	Patients with lactose induced symptoms (mm VAS)			Number (%) of patients with burdensome symptom		
Symptoms	**LM− (*n* = 445)**	**LM+ (*n* = 308)**	***p*-value LM− vs. LM+**	**LM− *n* (%)**	**LM+ *n* (%)**	***p*-value LM− vs. LM+**
Abdominal pain	16.4 ± 18.6	32.0 ± 26.1	**< 0.001**	66 (34.9)	144 (63.2)	**< 0.001**
Nausea	18.2 ± 21.9	16.9 ± 20.8	0.5	74 (39.2)	77 (33.8)	0.26
Bloating	19.9 ± 19.6	32.0 ± 25.9	**< 0.01**	86 (45.5)	135 (59.2)	**< 0.01**
Flatulence	16.4 ± 18.8	34.4 ± 27.5	**< 0.001**	72 (38.1)	154 (67.5)	**< 0.001**
Diarrhea	9.4 ± 19.8	33.2 ± 35.6	**< 0.001**	32 (16.9)	115 (50.4)	**< 0.001**
Total burden	80.3 ± 56.2	148.5 ± 88.6	**< 0.001**	189 (100)	228 (100)	—

Note: The mmVAS results from the aCPQ are presented as mean ± standard deviation to summarize the group data. Since not every single patient was positive in each of the five symptoms, the mean values for the whole group may fall below the 20 mm threshold that defines a burdensome symptom at the individual level. The rightmost part of the table displays the number of patients for whom each specific symptom was rated as burdensome. A p-value < 0.05 was considered significant and is printed in bold.
Abbreviations: LM+, lactose malabsorbers; LM−, lactose non-malabsorbers.

TABLE 2 | Number of patients (%) with positive or negative symptom response to fructose and positive or negative fructose H_2 breath test according to the result of lactose malabsorption and sensitivity testing in 547 patients who underwent both the lactose and fructose sensitivity/H_2-breath test.

	Lactose				
	L(S−M−) (*n* = 191)	**L(S+M−) (*n* = 137)**	**L(S−M+) (*n* = 53)**	**L(S+M+) (*n* = 166)**	**Sum (*n* = 547)**
Fructose					
FS−	**145 (41.3%)**	71 (20.2%)	40 (11.4%)	95 (27.1%)	351 (100%)
FS+	46 (23.5%)	**66 (33.7%)**	13 (6.6%)	**71 (36.2%)**	196 (100%)
p-Value (FS− vs. FS+)	**0.001**	**0.001**	0.1	**0.03**	
FM+	52 (31.3%)	30 (18.1%)	18 (10.8%)	**66 (39.8%)**	166 (100%)
FM−	139 (36.5%)	**107 (28.1%)**	35 (9.2%)	100 (26.3%)	381 (100%)
p-Value (FM− vs. FM+)	0.2	**0.01**	0.5	**0.002**	

Note: p Values below 0.05 are shown in bold. If the difference is significant, the group with the higher proportion of patients is shown in bold.
Abbreviations: FM+, fructose malabsorption; FM−, fructose absorption; FS+, sensitive to fructose challenge; FS−, asymptomatic to fructose challenge; L(S+M+), symptomatic lactose malabsorbers; L(S−M+), asymptomatic malabsorbers; L(S+M−), symptomatic non-malabsorbers; L(S−M−), asymptomatic non-malabsorbers.

TABLE 3 | The proportion of patients with disorders of the gut-brain interactions (in %) and IBS-SSS scores (± standard deviation, SD; patients with irritable bowel syndrome only) in relation to malabsorption and symptom status after lactose challenge.

	LS−		LS+	
	LM−	LM+	LM−	LM+
Functional dyspepsia (%)	61.0	**41.8**	72.1#	69.1#
Functional diarrhea (%)	**36.7**	29.1	23.6*	23.6*
Functional constipation (%)	16.2	**5.5**	15.7#	16.2#
Irritable bowel syndrome (%)	**28.6**	32.7	41.4*	41.4*
IBS-SSS (score ± SD)	190 ± 75	224 ± 67	190 ± 70	196 ± 78

Note: A dual diagnosis of functional dyspepsia and disease of the lower gastrointestinal tract is possible. IBS-SSS scores were not significantly different between the four groups.
*$p < 0.01$ versus L(S−M−), marked in bold.
#$p < 0.05$ versus L(S−M+), marked in bold.

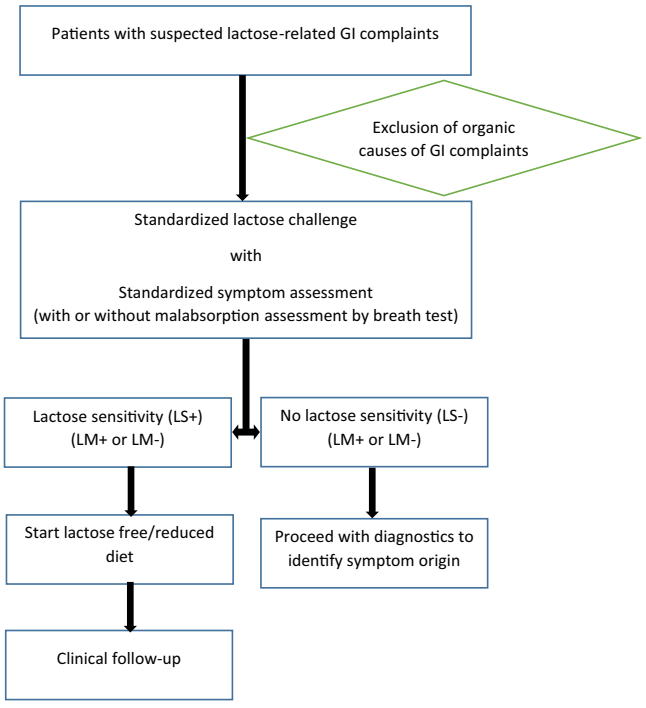

FIGURE 2 | Proposed diagnostic algorithm for lactose sensitivity. LM+, lactose malabsorbers; LM−, lactose non-malabsorbers; LS+, patients with lactose-induced symptoms; LS−, patients without lactose-induced symptoms.

depending on lactose malabsorption and symptoms (ANOVA test $p > 0.05$). The prevalence of disorders of the gut-brain interactions was not significantly different between the two symptomatic groups, L(S+M+) and L(S+M−) (Table 3, $p > 0.05$). In contrast, functional dyspepsia ($p < 0.01$) and functional constipation ($p < 0.05$) were significantly more frequent in LS+ (both LM+ and LM−) as compared to L(S−M+). IBS was significantly more common in LS+ with or without malabsorption than in L(S−M−) ($p < 0.01$). Functional diarrhea was less frequent in LS+ with or without malabsorption than in L(S−M−).

3.4 | Predictors of Symptom Response

A multivariate binary logistic regression was performed to identify independent predictors of symptom response to lactose ingestion (LS+). Lactose malabsorption (LM+) was a strong independent predictor of LS+ (OR = 5.37; 95% CI: 3.39–8.50; $p < 0.001$); fructose sensitivity (FS+) was also independently associated with LS+ (OR = 2.84; 95% CI: 1.79–4.48; $p < 0.001$). Fructose malabsorption showed a statistically significant but inverse association with symptoms (OR = 0.62; 95% CI: 0.38–0.99; $p = 0.047$). Age, gender, and the presence of IBS, functional diarrhea, or constipation were not significant independent predictors of lactose-induced symptoms in this model.

4 | Discussion

The results of this study indicate that in patients referred for the evaluation of abdominal symptoms suggestive of lactose as the etiology, a positive H_2BT indicating lactose malabsorption is not a good predictor of gastrointestinal symptoms following lactose ingestion. A significant proportion of patients without malabsorption exhibited clinically relevant burdensome symptoms, while a notable subset of patients with malabsorption remained asymptomatic. These findings challenge the conventional reliance on breath tests as the primary tool for diagnosing lactose intolerance and underscore the need for a more nuanced approach that includes symptom reporting (Figure 2).

Lactose breath tests have yielded a range of diagnostic accuracies for demonstrating lactose malabsorption. In studies using hydrogen alone with a 50-g lactose challenge, test sensitivities have ranged from 74% to 100% and specificities from 80% to 100% when the reference standard was a blood glucose response [15], genetic testing [16] or lactase activity [17, 18]. However, when compared with symptoms—as in our study—diagnostic performance of hydrogen breath tests is modest: we calculated from our data a test sensitivity of 54.6%, specificity of 76.2%, and a likelihood ratio of 2.29 for detecting lactose sensitivity. Thus, a positive breath test only moderately increases the likelihood of symptoms and is insufficient on its own for diagnosing clinically relevant lactose intolerance.

Our study corroborates previous research indicating that lactose malabsorption alone cannot explain the full spectrum of symptom experiences in individuals with lactose intolerance [19]. Similarly, in a Chinese population, a weak correlation between breath hydrogen levels and the severity of symptoms has been demonstrated [20]. This suggests that factors beyond carbohydrate malabsorption, such as visceral hypersensitivity, loss of intestinal barrier function, mast cell activation by luminal lipopolysaccharides [21], or altered gut microbiota [22], may play a critical role in symptom generation in patients with carbohydrate intolerance [23]. In line with these findings, our results

indicate that symptomatic lactose non-malabsorbers reported a notable symptom burden, suggesting mechanisms that are related to reactions of the small intestine to lactose, which may contribute to the development of symptomatology. One of these factors may be fluid inflow into the small intestine caused by the osmotic activity of the carbohydrate [24].

One possible explanation for the discrepancy between malabsorption and symptoms is a false negative H_2BT due to the role of hydrogen non-excretion, which may occur in up to 20% of individuals [25]. However, this cannot explain that 45.3% of patients with negative H_2BT had burdensome symptoms. A second possible explanation is visceral hypersensitivity, such as in irritable bowel syndrome (IBS). Individuals with heightened visceral sensitivity may experience significant discomfort when exposed to even small amounts of gas production or mild distension. It has been demonstrated that different carbohydrates can cause varying degrees of distension in the small and large intestine depending on the molecular size of the carbohydrate [26, 27]. This could explain why symptomatic lactose non-malabsorbers experienced substantial symptoms despite the absence of malabsorption. Furthermore, recent evidence points to gut microbiota as a potential mediator of gastrointestinal symptoms in patients with lactose sensitivity [28, 29]. Alterations in microbial composition can influence fermentation processes, production of histamine and other microbial mediators, and immune responses, potentially exacerbating symptoms independently of malabsorption [18].

We have recently demonstrated that a fructose challenge, when coupled with valid, test-specific symptom measurement, can serve as an indicator of visceral pain hypersensitivity [19]. The strong association between lactose-related symptoms and fructose sensitivity in our patients, irrespective of lactose malabsorption status, underscores the role of visceral hypersensitivity in symptom development following the lactose challenge, but also the potential for shared or overlapping mechanisms driving symptom generation. The possibility of a common underlying cause for lactose-related and fructose-related symptoms and DGBI, regardless of malabsorption, can be inferred from the distribution of DGBI, as their frequency was similarly distributed in lactose-symptomatic groups with and without malabsorption. Furthermore, certain DGBI, such as investigated functional dyspepsia and IBS, which are known to be related to visceral hypersensitivity [30, 31] were significantly more common in lactose-symptomatic patients compared to those with non-burdensome symptoms after the lactose challenge.

The use of the aCPQ in this study provided valuable insights into the patient-reported symptoms. The cut-off chosen is arbitrary as there is no known minimum clinically important difference in this area of research. The aCPQ identifies symptoms and symptom patterns, and offers a potential solution to the limitations of relying solely on H_2BT. Patient-reported outcomes are increasingly recognized as essential in understanding the true impact of gastrointestinal disorders. They reflect the patient's lived experience and can influence treatment decisions [4, 28]. The aCPQ has been validated for this purpose, and its application in this study reinforces its utility in capturing the symptom burden of lactose intolerance in adult patients. For patients younger than eighteen years, the Pediatric Carbohydrate Perception Questionnaire (pCPQ) has been validated [32, 33]. Both tests are available in several languages [34].

The findings of our study have important clinical implications. First, test-specific validated symptom assessment is a prerequisite for a personalized understanding of the relationship between symptom history, lactose malabsorption, and the symptoms caused by lactose consumption. Therefore, H_2BT shall not be the sole criterion for diagnosing lactose-induced complaints. These findings support the European guideline, which has recommended incorporating symptom assessment into lactose tolerance testing [4, 11]. Given that almost half of the symptomatic patients in our cohort did not exhibit malabsorption, it is evident that treatment strategies should not rely on breath test results but shall consider symptom burden [35]. Second, the high symptom burden reported by symptomatic lactose malabsorbers highlights the importance of treatment recommendations, which may include enzyme replacement therapy or tailored lactose restriction, independent of the underlying functional disorder. Third, malabsorbers who do not experience burdensome symptoms following high lactose exposure—50 g of lactose is equivalent to one liter of cow's milk—may benefit from symptom management strategies other than lactose restriction. The 50 g dose of lactose exceeds typical dietary intakes but is within the range of recommended doses to detect malabsorption [4]. Neither this dose nor any lower dose resembles a normal diet, which is made up of a complex mixture of carbohydrates and other food components. Previous research has shown that a dose of 50 g can serve as a reliable screening tool, potentially reducing unnecessary diagnostic procedures [36], though provoking stronger osmotic effects than dietary exposures. The choice of this dose is consistent with the aim of the study to assess lactose-induced symptom burden under test-specific conditions rather than simulating normal dietary intake. The 50 g dose allows effective screening for malabsorption and symptom assessment, providing a robust framework for understanding the relationship between hydrogen production and symptom burden. Finally, a history of symptoms that have caused the patient to be evaluated for lactose intolerance can only be correctly attributed to lactose if validated symptom measurement is performed after lactose ingestion—a positive result of a H_2BT alone is not sufficient to explain abdominal symptoms in these patients.

While our study focuses on the limited predictive value of lactose malabsorption for symptom burden, it is equally important to consider the clinical reality that patients typically present with symptoms, which then prompt testing. From this perspective, one could also argue that subjective lactose intolerance is a poor predictor of objective malabsorption, as many symptomatic individuals do not exhibit malabsorption on hydrogen breath testing. This reverse dissociation supports the growing recognition that symptoms may be driven by mechanisms other than malabsorption, including nocebo responses, anticipatory effects, or visceral hypersensitivity.

The poor correlation between objective lactose malabsorption (as measured by breath hydrogen testing) and subjective symptom burden challenges the current diagnostic paradigm for lactose intolerance. Our data show that nearly half of symptomatic patients do not malabsorb lactose, while a quarter of malabsorbers

are asymptomatic. This suggests that relying solely on breath tests to guide diagnosis and treatment decisions may lead to misclassification of the cause of symptoms and inappropriate dietary restrictions. However, breath testing is not without value: our results also demonstrate that when lactose malabsorption is present and associated with symptoms, the symptom burden is significantly higher than in non-malabsorbers with symptoms. This subgroup may represent patients in whom colonic fermentation is a key driver of symptoms and who are more likely to benefit from enzyme replacement or dietary restriction. Thus, the clinical value of breath tests lies not in their ability to predict symptoms in isolation, but rather in their use alongside validated, test-specific symptom assessment tools like the aCPQ. This combination allows for a more individualized interpretation of test results and enables clinicians to identify not only those who malabsorb lactose, but those for whom malabsorption is clinically relevant. In patients with symptoms but without malabsorption, alternative mechanisms such as visceral hypersensitivity may be at play, pointing toward different treatment strategies such as neuromodulators. Taken together, our findings support a more nuanced and patient-centered diagnostic algorithm for suspected lactose intolerance that integrates both objective and subjective data.

Our findings support a conceptual and clinical redefinition of the term "lactose sensitivity" to better capture the symptom response to lactose ingestion that occurs independently of measurable malabsorption [19]. We propose that "lactose sensitivity" be defined as the occurrence of reproducible, burdensome gastrointestinal symptoms after a standardized lactose challenge, irrespective of the presence or absence of lactose malabsorption as assessed by hydrogen breath testing. This contrasts with the traditional use of "lactose intolerance," which has often conflated the presence of symptoms with evidence of malabsorption. The term "sensitivity" is more appropriate for patients who exhibit symptoms without objective evidence of carbohydrate malabsorption, as this suggests the involvement of mechanisms other than colonic fermentation alone. Based on our results, diagnosis of lactose sensitivity should include (1) a standardized lactose challenge, (2) concurrent validated symptom assessment using tools such as the aCPQ, and (3) documentation of a burdensome symptom response (Figure 2). By decoupling symptom generation from the requirement of malabsorption, this definition allows clinicians to identify a broader and clinically meaningful group of patients who may benefit from treatment—despite normal breath test results. It also aligns with recent guideline recommendations to incorporate symptom monitoring into diagnostic work-up and paves the way for more individualized management strategies in clinical practice. Historically, the terminology surrounding lactose intolerance has been a source of confusion. The term has often been used interchangeably with lactose malabsorption, despite the poor correlation between malabsorption and the symptoms triggered by lactose ingestion, as demonstrated in the present study. Given the growing evidence that factors other than malabsorption may play a key role in the development of symptoms after lactose ingestion, it may be more appropriate to adopt the term "lactose sensitivity" [19]. This term better reflects the broader spectrum of pathophysiological mechanisms involved. Adopting this revised term may enhance our understanding of the etiology of lactose related symptoms and improve diagnostic accuracy in clinical practice.

The strengths of this study lie in its large sample size coming from two expert centers, the use of the validated aCPQ for symptom assessment, and the rigorous testing methodology employed as recommended by the European Guideline, which included both lactose and fructose challenges. These elements allowed for a detailed analysis of symptom burden and its relationship to malabsorption. Although the population includes patients with various forms of DGBIs, the common feature of symptomatology suggestive to the referring physicians for carbohydrate intolerance unites this cohort. This shared characteristic underscores the importance of exploring mechanisms, such as visceral hypersensitivity and carbohydrate malabsorption, that contribute to symptom burden across these disorders. However, as a referred cohort, the study population is subject to indication bias, likely skewed toward individuals with a high pretest probability of symptoms. Moreover, recruitment from two tertiary care centers may contribute to selection bias, as these patients could differ systematically from those seen in primary care or general population settings in terms of symptom severity, complexity, or health-seeking behavior.

However, the study has some limitations. First, we did not include a placebo challenge in this trial, so we cannot rule out a nocebo effect. The absence of a placebo-controlled challenge limits the ability to definitively attribute symptoms to lactose ingestion, as nocebo responses or background symptom fluctuations cannot be excluded. Future studies incorporating blinded, placebo-controlled designs are needed to better establish causality. Second, we did not assess psychological factors such as anxiety, attention to visceral cues, and illness behavior. This was because including these factors might have introduced selection bias, favoring patients willing to undergo a more comprehensive evaluation. Third, while the test design allowed for the identification of symptoms associated with carbohydrate ingestion, mechanistic biomarkers such as oro-cecal transit, intestinal permeability, inflammation, or microbiome profile were not investigated. Their inclusion could have provided additional insight into non-malabsorptive symptom pathways. Fourth, although the aCPQ is a validated instrument for assessing test-specific symptoms, the >20 mm VAS cut-off for defining a burdensome symptom has not undergone formal validation. This means that it may be either overly sensitive or not sensitive enough. This could lead to symptoms being either over- or underreported. Further research is required to establish clinically meaningful thresholds that balance sensitivity and specificity. Fifth, not all patients underwent fructose testing; test allocation was based on clinical judgment. However, differences in patient characteristics between those who underwent single versus dual testing were minor and deemed clinically irrelevant.

Finally, the lack of methane measurement in the lactose breath test may be considered a limitation, as the presence of methane-producing bacteria may result in hydrogen non-excretion [37] which may reduce the sensitivity of H2BT for diagnosing lactose malabsorption [21]. Up to 20% of the healthy population produce methane, which in breath tests is detected as baseline methane concentration, and one molecule of methane binds four molecules of hydrogen. Therefore, methane production may be one of several possible reasons for an absence of an increase in breath hydrogen excretion in carbohydrate malabsorption which is termed hydrogen non-excretion [38]. Reports

on the prevalence of hydrogen non-excretion after ingestion of the test sugar lactulose range from 10% to 20% [21, 39] but do not come close to the proportion of patients with lactose intolerance who had negative hydrogen breath tests in our study, which was 45%. Furthermore, it has previously been demonstrated that measuring an increase in breath methane concentration, in addition to breath hydrogen, only raises the detection rate of carbohydrate malabsorption by 4%, which is not significant [40]. Of the patients in our present population, 175 underwent a breath test involving both hydrogen and methane (see Table S3). Thirteen percent reached a methane level of over 5 ppm during the breath test (i.e., they were 'CH_4-producers'). In no patient (0%) was the diagnosis of lactose absorption based solely on CH_4 production. The nuanced interpretation of the role of methane measurement among researchers does not take into account the recent detailed analysis of the limited importance as described in the European Guideline on breath tests [5], but this is understandable given the historical focus on breath hydrogen and methane measurements for malabsorption, SIBO or orocecal transit [41], all of which have been questioned recently [5, 42]. We agree that further research is needed to confirm the role of methane measurement in diagnosing carbohydrate malabsorption. However, we suggest that for clinical purposes, that is identifying the cause of symptoms and identifying the patients who are likely to benefit from specific treatments directed at intolerances or sensitivities, like diet or food supplements, increased carbohydrate sensitivity requires more scientific attention in the future.

5 | Conclusion

In conclusion, our findings highlight the inadequacy of relying solely on lactose malabsorption to predict symptom burden in patients with suspected lactose intolerance. The integration of patient-reported outcomes, such as those obtained through the aCPQ, provides a more comprehensive assessment and may improve the management of this condition. Lactose-induced symptoms often occur in the absence of lactose malabsorption. Relying solely on hydrogen breath testing may misclassify the cause of symptoms in patients and overlook clinically relevant symptom burdens. We propose a redefinition of "lactose sensitivity" as burdensome, reproducible symptoms following a standardized lactose challenge, independent of malabsorption status. Integrating validated symptom assessment into diagnostic practice is essential for accurate diagnosis and personalized management. Diagnosis should involve a standardized lactose challenge, validated symptom assessment (e.g., aCPQ), and documented burdensome response.

Future research should explore the underlying mechanisms driving symptoms in non-malabsorbers and investigate therapeutic strategies that address both the physiological and perceptual components of lactose intolerance. Future studies utilizing functional assessment such as small bowel volume or transit time may shed further light on the mechanisms of carbohydrate symptoms beyond malabsorption. Moreover, establishing validated thresholds for symptom burden scores with validated instruments like the aCPQ will be essential to avoid potential overestimation of clinically relevant responses.

Author Contributions

Johann Hammer: study concept and design; study supervision; statistical analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript. **Heinz F. Hammer:** study design, acquisition of data, administrative, technical, or material support, interpretation of data; critical revision of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** nmo70167-sup-0001-DataS1.pdf.