SYSTEMATIC REVIEW

DOI: http://dx.doi.org/10.15403/jgld-5836

Self-Perceived Lactose Intolerance Versus Confirmed Lactose Intolerance in Irritable Bowel Syndrome: A Systematic Review

Andrei Pop[1], Stefan Lucian Popa[1], Dalina Diana Pop[2], Abdulrahman Ismaiel[1], Vlad Ionut Nechita[3], Dan L. Dumitrascu[1]

1) 2nd Medical Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca;
2) Department of Anatomy and Embryology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca;
3) Department of Medical Informatics and Biostatistics, Faculty of Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Address for correspondence:
Stefan Lucian Popa
2nd Medical Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
popa.stefan@umfcluj.ro

Received: 29.07.2024
Accepted: 23.08.2024

ABSTRACT

Background & Aims: Disorders of gut-brain interaction (DGBI) are prevalent, affecting 20-40% of the population, with irritable bowel syndrome (IBS) being the most common and impactful. While congenital lactose intolerance is rare, lactase deficiency in adults is widespread, causing gastrointestinal symptoms like bloating and diarrhea. Self-perceived lactose intolerance often overestimates symptoms, impacting dietary choices and quality of life, necessitating better understanding and management for improved patient outcomes. This article evaluates the diagnostic accuracy of self-reported lactose intolerance in patients with lactose intolerance and IBS through a systematic review.

Methods: A systematic literature search was conducted using PubMed, EMBASE, and SCOPUS, including terms related to IBS, lactose intolerance, and self-reported symptoms, without applying filters to ensure comprehensive coverage. Inclusion criteria focused on observational studies with adult participants diagnosed with lactose intolerance, addressing symptoms and lactose malabsorption, while excluding non-English articles, reviews, editorials, and studies involving pediatric subjects.

Results: The systematic review analyzed six studies with 845 participants, revealing significant variability and moderate accuracy in self-reported lactose intolerance for diagnosing actual lactose intolerance in IBS patients. Hydrogen breath tests (HBTs) showed that self-reported symptoms often led to false positives, underscoring the need for objective diagnostic tools and standardized criteria. The findings highlight the complexity of diagnosing lactose intolerance in IBS patients and suggest that lactose-free diets and routine HBT should not be recommended without clear indications.

Conclusions: The rigorous selection process ensured the inclusion of high-quality, relevant studies, thereby enhancing the reliability and validity of the review's findings. These studies revealed that a lactose-free diet should not be routinely recommended for IBS patients, nor should the routine use of HBT to identify lactose malabsorption in this group. Future research should focus on better understanding the factors influencing lactose perception and tolerance, which is crucial for more effective management of lactose intolerance in IBS patients.

Key words: lactose intolerance – lactose malabsorbtion – hydrogen breath test – irritable bowel syndrome – lactose-free diet.

Abbreviations: DGBI: disorder of gut-brain interaction; HBT: hydrogen breath test; IBS: irritable bowel syndrome.

INTRODUCTION

Disorder of Gut-Brain Interaction (DGBI) are a commonly group of disorders related to digestion, with a prevalence ranging from 20% to 40% among the general population [1]. Among these disorders, the most frequently occurring and researched one is the irritable bowel syndrome (IBS), which affects a significant portion of the population, with a global prevalence around 9-11%, significantly affecting their quality of life [2].

In Europe, the frequency of primary late-onset lactase deficiency exhibits considerable variability across different regions. For instance, only about 2% of the population in Scandinavia is affected, whereas in certain regions of Italy, the prevalence can be as high as 70% [3]. This broad range can be attributed to a combination of genetic, dietary, and

cultural factors. Scandinavian populations have historically consumed a diet rich in dairy products, which may have influenced genetic selection for lactase persistence [4, 5]. In contrast, some Italian regions have dietary patterns that do not rely as heavily on dairy, leading to higher rates of lactase deficiency. These genetic differences are further compounded by cultural practices and dietary habits that either promote or reduce lactose consumption [6].

Comparatively, in the United States, approximately 20% of the white population experiences lactase deficiency, underscoring significant variation between ethnic groups [3]. This disparity in lactase deficiency prevalence between European and American populations illustrates the influence of genetic diversity and migration patterns on lactose tolerance. Different ethnic groups in the United States bring their unique genetic predispositions, which affects the overall prevalence of lactase deficiency. Understanding these variations is crucial for developing region-specific dietary recommendations and for improving the management of lactose intolerance across diverse populations [7, 8].

Lactose is the primary carbohydrate in infant nutrition, playing a crucial role in the early stages of life. Congenital lactose intolerance, an extremely rare condition, presents itself from birth due to a genetic inability to produce lactase, the enzyme necessary for lactose digestion [9]. The condition manifests as severe and intractable diarrhea during the neonatal period, occurring shortly after the intake of human milk or lactose-containing milk formula. The diarrhea is often accompanied by other signs of gastrointestinal distress, such as abdominal bloating, gas, and discomfort, which can lead to dehydration and poor weight gain if not properly managed [10]. Lactose malabsorption can also occur temporarily due to secondary causes like infectious gastroenteritis, cow's milk allergy, and celiac disease. Once these underlying conditions are addressed, lactase activity typically returns to normal levels, allowing for the proper digestion of lactose [11, 12].

Lactase deficiency and resulting lactose malabsorption are frequent among adults, affecting between from 4% up to 56% of the European population [13]. This condition is linked to various gastrointestinal symptoms, including abdominal distention, flatulence, abdominal cramping, and diarrhea. These symptoms occur due to the inability to properly digest lactose, a sugar found in milk and dairy products, leading to its fermentation by gut bacteria. Despite the discomfort it causes, health providers often regard lactase deficiency as a minor condition [14, 15]. In the small intestine, the enzyme lactase breaks down lactose into two monosaccharides for absorption. If there is a deficiency or absence of lactase, lactose moves to the large intestine, where bacteria break it down, producing gases like hydrogen. This hydrogen is then absorbed into the bloodstream, exhaled through the lungs, and measured using a hydrogen breath test (HBT) [16].

The self-lactose intolerance perception can have a high prevalence among different populations, but generally low severity of symptoms, which are often manageable with dietary adjustments. Additionally, there is a lack of correlation with objective measures of lactase activity or lactose absorption, further contributing to its underestimation in clinical settings. Understanding the impact of lactase deficiency is crucial for improving patient outcomes, as even mild symptoms can significantly affect quality of life [17].

Daily-life symptoms that patients associate with lactose intolerance are often unrelated to lactose malabsorption. Even in true lactose malabsorbers, the recall of symptoms tends to be amplified by the patient. This tendency to overestimate the severity and frequency of symptoms is significant, as it influences dietary habits and overall health [18]. Intolerant individuals experience symptoms due to poor digestion and malabsorption of lactose. Symptoms typically appear 30 minutes to 2 hours after intake and include diarrhea, soft-liquid stools, and accelerated intestinal transit caused by lactose-induced osmotic pressure. Fermentation leads to gas, resulting in abdominal distension, pain, cramps, postprandial fullness, burping, nausea, and acidic stools with perianal erythema [19, 20].

The aim of this article is to systematically evaluate the diagnostic accuracy of self-reported lactose intolerance in patients with lactose intolerance and IBS through a comprehensive analysis. This article intends to underscore the need for accurate diagnostic practices to enhance patient management and outcomes in clinical settings.

METHODS

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020 [21].

A systematic literature search was conducted using the databases PubMed, EMBASE, and SCOPUS from their inception until June 2024. The search strategy incorporated the following terms: ((„Irritable Bowel Syndrome"[Mesh]) OR („Irritable Bowel Syndrome"[All Fields])) AND ((„Lactose Intolerance"[Mesh]) OR („Lactose Intolerance"[All Fields])) AND ((„Self Report"[Mesh]) OR („Self Report"[All Fields]) OR („Perception"[Mesh]) OR („Perception"[All Fields]) OR („self reported") OR („self report") OR („perceived")). No filters were applied to the search to ensure a comprehensive collection of relevant studies.

The inclusion criteria for this systematic review were observational studies that focused on adult populations, specifically individuals aged 18 years and older. The selected studies required participants to have a confirmed diagnosis of lactose intolerance. Furthermore, the studies needed to address the manifestation of symptoms associated with lactose intolerance as well as indicators of lactose malabsorption.

In contrast, the exclusion criteria were designed to not include sources that may not contribute to a comprehensive and rigorous analysis. This included abstracts and conference presentations, case reports, and articles published in languages other than English. Additionally, reviews, editorials, letters to the editor, books, and studies involving pediatric subjects were excluded from consideration. This selective approach aimed to ensure that the included studies provided high-quality, relevant data, thus enhancing the reliability and validity of the review's findings.

To assess the methodological quality of the studies included in our systematic review and meta-analysis, we used the Newcastle-Ottawa Scale (NOS). This tool allowed us to evaluate

the quality of cross-sectional studies based on several criteria including sample representativeness, sample size justification, handling of non-respondents, ascertainment of exposure, control for confounding variables, assessment of outcomes, and appropriateness of statistical tests [22].

RESULTS

The literature search identified a total of 185 records across the databases. Following the removal of 27 duplicate records, 158 unique records remained for further screening. The initial screening process led to the exclusion of 104 records based on title and abstract review, leaving 54 records for detailed examination.

These 54 records were then subjected to a thorough screening of the full-text articles, which resulted in the exclusion of 36 additional records. The primary reasons for exclusion at this stage included not meeting the inclusion criteria or presenting inadequate data for analysis.

Eighteen full-text articles were assessed for eligibility. Of these, 12 articles were excluded for various reasons, such as failing to meet the predefined inclusion criteria or providing insufficient data. Consequently, six studies [16, 23-27] were deemed eligible and included in the qualitative synthesis of this systematic review (Fig. 1).

Sample Size, Demographics And Gender Distribution

The analysis of six studies on lactose intolerance involved 845 participants, with sample sizes ranging from 51 to 402. The mean age of participants was generally in the mid-30s to mid-40s. This age range indicates a focus on middle-aged adults, where lactose intolerance symptoms are more commonly reported (Table I).

The gender distribution across the six studies varied significantly. Out of 845 participants, 39.3% were male and 60.7% were female. Gupta et al. [24] had a predominantly male sample (73%), while Dainese et al. [16] had a predominantly female sample (80.4%). Yang et al. [25] and Xiong [26] had a more balanced gender distribution (Table II).

Lactose Tolerance and Intolerance

The HBT results showed that among the participants, 230 (27.2%) were HBT positive and lactose tolerant, 319 (37.7%) were HBT positive and lactose intolerant, 135 (16%) were HBT negative and lactose tolerant, and 134 (15.9%) were HBT negative and lactose intolerant (Fig. 2).

Sensitivity and Specificity

The cross-study analysis conducted on the sensitivity and specificity of self-perceived lactose intolerance for diagnosing actual lactose intolerance demonstrated notable variations and patterns across the examined studies. The calculated sensitivities and specificities varied among the studies. The sensitivity ranged from 45% [26] to 75.6% [23], while the specificity ranged from 14.5% [26] to 46.6%. The pooled sensitivity was determined to be 67.8%, indicating a moderate ability to correctly identify individuals with lactose intolerance. In contrast, the pooled specificity was 35.7%, reflecting a lower accuracy in correctly identifying individuals without lactose intolerance, thus indicating a considerable number of false positives.

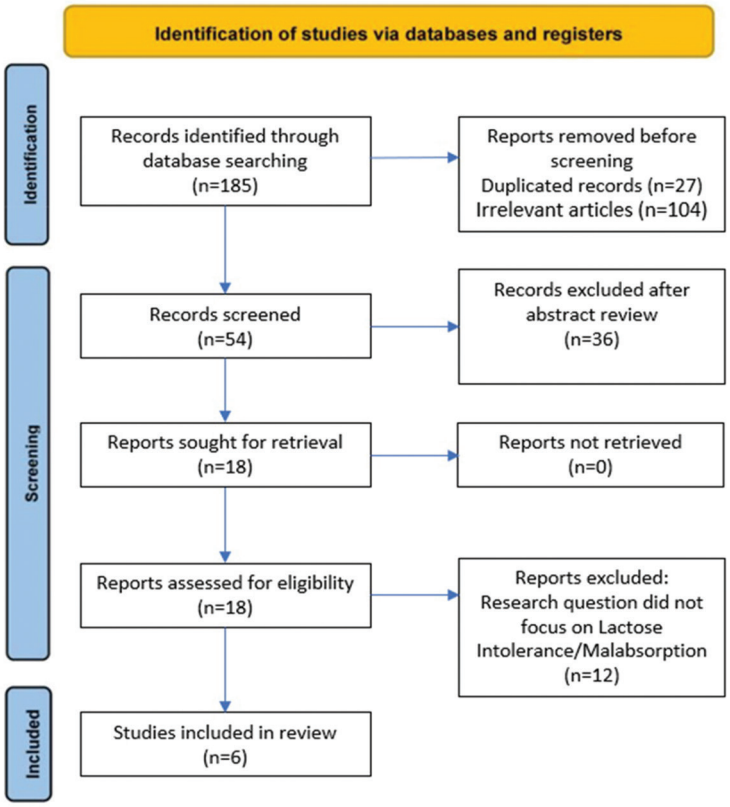

Fig. 1. PRISMA flowchart of the included studies.

Table I. Comparative summary table

Article	Study Focus	Population and Sample Size	Methodology	Key Findings
Vernia et al, 2004 [23]	Self-reported milk intolerance in IBS	402 IBS patients (Rome criteria), matched pairs analysis	Hydrogen breath test	Self-reported milk intolerance is unreliable in predicting lactose malabsorption
Gupta et al, 2007 [24]	Frequency of LI in IBS patients	127 IBS patients (Rome criteria),	Case-control study	Significant overlap of symptoms between IBS and LI; specific symptoms not detailed
Yang et al, 2013 [25]	Prevalence and effects of LI on dairy intake	60 IBS patients (Rome criteria),	Survey and clinical evaluation	Common symptoms include abdominal pain, bloating, flatulence, and diarrhea;
Dainese et al, 2014 [16]	Perception of lactose intolerance in IBS	51 IBS patients (Rome criteria)	Hydrogen breath test	Discrepancy between perceived and confirmed lactose intolerance
Xiong et al, 2017 [26]	Prevalence of LI in IBS-D patients	109 IBS-D patients and 50 healthy controls in Southern China	Hydrogen breath test	Higher prevalence of LI in IBS-D patients compared to healthy subjects; self-reported milk intolerance is unreliable
Bouchoucha et al, 2020 [27]	Various gastrointestinal motility studies	154 IBS patients	Multiple methodologies	Covers a broad range of studies related to IBS and other gastrointestinal disorders

IBS: irritable bowel syndrome; IBS-D: diarheea predominant IBS; LI: lactose intolerance.

The graphical representation of these findings (Fig. 3) provides a visual comparison of sensitivity and specificity across the studies. Each bar represents the sensitivity or specificity of an individual study, with the red dashed line indicating the pooled value. This visual aid underscores the variability among studies and highlights the overall performance metrics, emphasizing the moderate sensitivity and relatively low specificity of self-perceived lactose intolerance as a diagnostic tool.

Symptoms in IBS and Lactose Intoleance Patients

The comparative analysis of symptoms in IBS and lactose intolerance patients across multiple studies reveals several key findings. This analysis underscores the challenge of differentiating IBS from lactose intolerance based on symptoms alone and highlights the need for further research to improve diagnostic accuracy (Table III).

Quality of Assessment

To assess the methodological quality of the studies included in our systematic review and meta-analysis, the Newcastle-Ottawa Scale (NOS) was used, as described in Table IV. A total of 6 articles were assessed through the NOS criteria.

Overall, all the cross-sectional studies had a clearly stated research aim or question. On the other hand, all the included studies did not clearly specify or define the study population. None of the investigators were able to confirm that the exposure or risk occurred prior to the development of the conditions. The independent variables were clearly defined, valid, and reliable, and implemented consistently across all participants in all the previously mentioned studies. Regarding the cross-sectional studies, we found that only half of them adjusted for key confounding variables.

None of the cross-sectional studies assessed exposures more than once over time. All the studies had representative samples of the clinical population of interest; all their participants that met the prespecified entry criteria were enrolled and were with a sufficient sample size to provide confidence in their findings except for one study.

These evaluations provided a detailed assessment of the methodological quality of the included studies, highlighting areas of strength and those requiring improvement.

Table II. Patient demographics and hydrogen breath test (HBT) data across multiple studies

First Author	HBT Positive Tolerant	Total Tolerant	HBT Negative Tolerant	HBT Positive Intolerant	Total Intolerant	Total Patients	HBT Negative Intolerant	Mean Age (years)	Gender (% Male)	Gender (% Female)
Vernia et al, 2004 [23]	138	201	63	152	201	402	49	35.7 ± 14.4	29.8	70.2
Gupta et al, 2007 [24]	43	56	13	49	56	124	7	35.5 ± 11.1	73.0	27.0
Yang et al, 2013 [25]	17	22	5	34	38	60	4	40.8 ± 11.7	48.3	51.7
Dainese et al, 2014 [16]	14	37	23	7	14	51	7	45 ± 16	19.6	80.4
Xiong et al, 2017 [26]	18	49	31	25	47	109	22	36.0 ± 12.2	52.3	47.7
Bouchoucha et al, 2020 [27]				54	99	99	45	41.6 ± 15.8	27.0	73.0

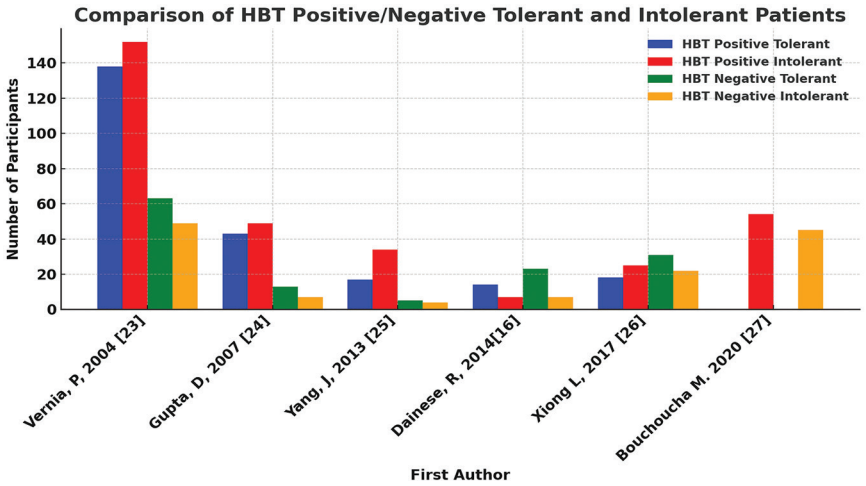

Fig. 2. Distribution of Participants by HBT data Across Multiple Studies. This figure illustrates the number of participants categorized as HBT Positive Tolerant, HBT Positive Intolerant, HBT Negative Tolerant, and HBT Negative Intolerant across six different studies (Vernia P. 2004, Gupta D. 2007, Yang J. 2013, Dainese R. 2014, Xiong L. 2017, and Bouchoucha M. 2020). The bars represent the participant count for each tolerance status within each study.

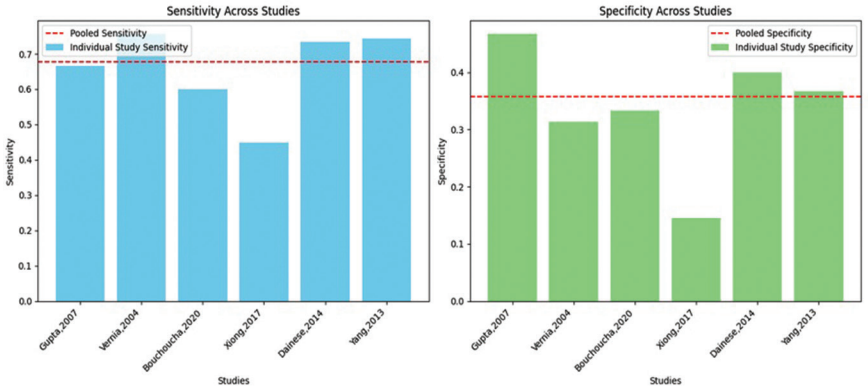

Fig. 3. Sensitivity and Specificity Across Studies The left panel shows the sensitivity of each study, with individual study sensitivities indicated by blue bars and the pooled sensitivity marked by the red dashed line. The right panel illustrates the specificity of each study, with individual study specificities shown by green bars and the pooled specificity indicated by the red dashed line. These panels compare the diagnostic performance of different studies on sensitivity and specificity metrics.

Table III. Comparative symptoms in IBS and lactose intolerance patients

Article	Symptoms in IBS Patients	Symptoms in lactose intolerance patients
Vernia et al, 2004 [23]	Flatulence, pain, bowel movements with loose stools	Similar symptoms as IBS patients
Gupta et al, 2007 [24]	Overlap of symptoms between IBS and lactose intolerance;	Overlap of symptoms between IBS and lactose intolerance
Yang et al, 2013 [25]	Abdominal pain, bloating, flatulence, diarrhea	Abdominal pain, bloating, flatulence, diarrhea
Dainese et al, 2014 [16]	Severe symptoms	Moderate symptoms
Xiong et al, 2017 [26]	Abdominal pain, bloating, borborygmi, diarrhea	Abdominal pain, bloating, borborygmi, diarrhea
Bouchoucha et al, 2020 [27]	IBS-D – severe symptoms than lactose intolerance	Nausea, bloating, diarrhea, borborygmi, abdominal pain

Table IV. The Newcastle-Ottawa Scale (NOS) for assessing the quality of cross-sectional studies

Study	Sample representativeness	Sample size	Non-Respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	Score
Vernia et al, 2004 [23]	*	*		*	**	**	*	8
Gupta et al, 2007 [24]	*	*		*	**	**	*	8
Yang et al, 2013 [25]	*	*		*	**	**	*	8
Dainese et al, 2014 [16]	*			*	**	**	*	7
Xiong et al, 2017 [26]	*	*		*	**	**	*	8
Bouchoucha et al, 2020 [27]	*	*		*	**	**	*	8

DISCUSSION

The cumulative analysis of these six studies reveals significant variability in sample sizes, age distributions, and gender proportions. The findings underscore the high prevalence of lactose intolerance across different populations. The HBT results indicate that a substantial proportion of participants experienced lactose intolerance, emphasizing the need for effective dietary and clinical management strategies. This comprehensive understanding of lactose intolerance across diverse demographics enhances the overall knowledge and informs better health practices and interventions.

These values indicate that self-perceived lactose intolerance has moderate sensitivity, meaning a correct identification of approximately 68% of those who are truly lactose intolerant. However, it has low specificity, meaning it only correctly identifies about 36% of those who are not lactose intolerant, indicating a significant number of false positives. This suggests that while many individuals who perceive themselves as lactose intolerant are indeed so, a substantial number of individuals may incorrectly perceive themselves as lactose intolerant.

The examination of the deviation of each study's sensitivity and specificity from the pooled values highlighted systematic trends. Studies such as Vernia et al. [23], Dainese et al. [16], and Yang et al. [25] showed a positive deviation in sensitivity, suggesting a potential overestimation in their ability to detect true positives. Conversely, Gupta et al [24], Bouchoucha et al [27], and Xiong et al. [26] exhibited a negative deviation, indicating an underestimation. For specificity, Gupta et al. [24], Dainese et al. [16], and Yang et al. [25] demonstrated a positive deviation, while Vernia et al. [23], Bouchoucha et al. [27], and Xiong et al. [26] showed a negative deviation, pointing to a potential overestimation of true negatives.

Some studies did not find any significant differences in the prevalence of lactose malabsorption between IBS patients and non-IBS controls [23, 28]. However, another study indicated that lactose malabsorption was not necessarily the cause of self-reported lactose intolerance [18]. Many patients with IBS reported self-perceived lactose intolerance before any objective tests, but the prevalence of lactose malabsorption in this group was similar with general population [25].

The gender distribution across the six studies exhibited a notable imbalance, with 39.3% of the 845 participants being male and 60.7% being female. This significant variation highlights the critical need for gender-specific analysis in lactose intolerance research. The disproportionate representation of females may indicate potential differences in the prevalence and severity of lactose intolerance symptoms between genders. Understanding these gender-based differences is essential, as it can inform more tailored and effective diagnostic and treatment strategies [29]. Moreover, it raises questions about the underlying biological, genetic, and hormonal factors that might contribute to these discrepancies, emphasizing the need for further in-depth studies to explore these dynamics. Such gender-focused research can ultimately lead to improved health outcomes by ensuring that both men and women receive accurate diagnoses and appropriate care for lactose intolerance.

Moreover, it raises questions about the underlying biological, genetic, and hormonal factors that might contribute to these discrepancies, emphasizing the need for further in-depth studies to explore these dynamics. Such gender-focused research can ultimately lead to improved health outcomes by ensuring that both men and women receive accurate diagnoses and appropriate care for lactose intolerance.

Despite the potential for digestive discomfort, unabsorbed lactose offers significant health benefits. One of the most notable advantages is its bifidogenic effect, which promotes the growth of beneficial bifidobacteria in the gut [30]. These beneficial bacteria play a crucial role in maintaining a healthy intestinal flora, enhancing gut health, and supporting the immune system. Furthermore, unabsorbed lactose improves calcium absorption, which is essential for maintaining strong bones and teeth, and overall skeletal health. By fostering a balanced gut microbiome and enhancing nutrient absorption, unabsorbed lactose contributes positively to digestive and overall health, even in the presence of mild digestive disturbances [13, 31].

Many people with clinically confirmed lactose intolerance can still consume dairy foods with proper guidance to meet nutrient recommendations. Research indicates that those who perceive themselves as lactose intolerant can often consume dairy without symptoms. For instance, one study found that

lactose-intolerant individuals can tolerate up to 2 cups (≈474 mL) of milk per day when consumed with meals [32, 33].

Diagnosing food intolerance is challenging for clinicians, as many patients experience symptoms after eating and often blame various foods, believing they are „intolerant to all foods". These patients frequently misinterpret their symptoms and self-diagnose with a food intolerance that typically doesn't exist; instead, their symptoms are usually due to DGBI. Contributing to this misinterpretation are the overlap of intolerance symptoms with those of DGBI and the lack of validated diagnostic tests for food intolerances [34-36].

Furthermore, the avoidance of dairy without proper medical advice can lead to unnecessary dietary restrictions and potential nutrient deficiencies. It is important for healthcare providers to accurately diagnose lactose intolerance and educate patients on managing their symptoms without compromising their nutritional status [11].

CONCLUSIONS

The studies collectively emphasize the complexity of diagnosing and managing lactose intolerance in patients with IBS. The findings strongly advocate for the use of objective diagnostic tools like HBT over self-reported symptoms to ensure accurate diagnosis and effective management. The observed biases and systematic trends in sensitivity and specificity values across studies suggest inherent inconsistencies in assessing self-perceived lactose intolerance, underscoring the need for standardized diagnostic criteria and further research to enhance diagnostic accuracy in clinical practice.

Additionally, the studies indicate that a lactose-free diet should not be routinely recommended for IBS patients. Similarly, routine use of HBT to identify lactose malabsorption in IBS patients is not advised. Future investigations should focus on gaining a better understanding of the factors involved in lactose perception and tolerance. This improved comprehension is clinically relevant and deserve consideration due to its implications for more effective management of lactose intolerance in IBS patients.

Conflicts of interest: None to declare.

Authors' contributions: A.P., S.L.P and D.L.D. conceived and designed the study. A.P., D.D.P., A.I. and V.I.N. contributed to the acquisition, analysis and interpretation of data. A.P. and S.L.P drafted the manuscript. S.L.P and D.L.D. critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology 2021;160:99-114.e3. doi:10.1053/j.gastro.2020.04.014
2. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 2017;66:1075–1082. doi:10.1136/gutjnl-2015-311240
3. Ozdemir O, Mete E, Catal F, Ozol D. Food Intolerances and Eosinophilic Esophagitis in Childhood. Dig Dis Sci 2009;54:8–14. doi:10.1007/s10620-008-0331-x
4. Stock JT, Wells JCK. Dairying and the evolution and consequences of lactase persistence in humans. Anim Front 2023;13:7–13. doi:10.1093/af/vfad022
5. Evershed RP, Davey Smith G, Roffet-Salque M, et al. Dairying, diseases and the evolution of lactase persistence in Europe. Nature 2022;608:336–345. doi:10.1038/s41586-022-05010-7
6. Swallow DM. Genetics of Lactase Persistence and Lactose Intolerance. Annu Rev Genet 2003;37:197–219. doi:10.1146/annurev.genet.37.110801.143820
7. Bayless TM, Brown E, Paige DM. Lactase Non-persistence and Lactose Intolerance. Curr Gastroenterol Rep 2017;19:23. doi:10.1007/s11894-017-0558-9
8. Dzialanski Z, Barany M, Engfeldt P, Magnuson A, Olsson LA, Nilsson TK. Lactase persistence versus lactose intolerance: Is there an intermediate phenotype? Clin Biochem 2016;49:248–252. doi:10.1016/j.clinbiochem.2015.11.001
9. Toca MDC, Fernández A, Orsi M, Tabacco O, Vinderola G. Lactose intolerance: myths and facts. An update. Arch Argent Pediatr 2022;120:59–66. doi:10.5546/aap.2022.eng.59
10. Diekmann L, Pfeiffer K, Naim HY. Congenital lactose intolerance is triggered by severe mutations on both alleles of the lactase gene. BMC Gastroenterol 2015;15:36. doi:10.1186/s12876-015-0261-y
11. Barr SI. Perceived lactose intolerance in adult Canadians: a national survey. Appl Physiol Nutr Metab 2013;38:830–835. doi:10.1139/apnm-2012-0368
12. Al-Beltagi M, Saeed NK, Bediwy AS, Elbeltagi R. Cow's milk-induced gastrointestinal disorders: From infancy to adulthood. World J Clin Pediatr 2022;11:437-454. doi:10.5409/wjcp.v11.i6.437
13. Casellas F, Aparici A, Pérez MJ, Rodríguez P. Perception of lactose intolerance impairs health-related quality of life. Eur J Clin Nutr 2016;70:1068–1072. doi:10.1038/ejcn.2016.80
14. Cangemi DJ, Lacy BE. A Practical Approach to the Diagnosis and Treatment of Abdominal Bloating and Distension. Gastroenterol Hepatol (N Y) 2022;18:75.
15. Martínez Vázquez SE, Nogueira de Rojas JR, Remes Troche JM, Coss Adame E, Rivas Ruíz R, Uscanga Domínguez LF. The importance of lactose intolerance in individuals with gastrointestinal symptoms. Rev Gastroenterol Mex (Engl Ed) 2020;85:321–331. doi:10.1016/j.rgmx.2020.03.002
16. Dainese R, Casellas F, Mariné-Barjoan E, et al. Perception of lactose intolerance in irritable bowel syndrome patients. Eur J Gastroenterol Hepatol 2014;26:1167–1175. doi:10.1097/MEG.0000000000000089
17. Argüelles Arias F, Rodríguez Ledo P, Tenias JM, et al. The management of lactose intolerance among primary care physicians and its correlation with management by gastroenterologists: the SEPD-SEMG national survey. Rev Esp Enferm Dig 2015;107:554-558. doi:10.17235/reed.2015.3771/2015
18. Casellas F, Aparici A, Casaus M, Rodríguez P, Malagelada JR. Subjective perception of lactose intolerance does not always indicate lactose malabsorption. Clin Gastroenterol Hepatol 2010;8:581–586. doi:10.1016/j.cgh.2010.03.027
19. DI Costanzo M, Berni Canani R. Lactose Intolerance: Common Misunderstandings. Ann Nutr Metab 2019;73 Suppl 4:30–37. doi:10.1159/000493669

20. Szilagyi A, Ishayek N. Lactose Intolerance, Dairy Avoidance, and Treatment Options. Nutrients 2018;10:1994. doi:10.3390/nu10121994
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89. doi:10.1186/s13643-021-01626-4
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–605. doi:10.1007/s10654-010-9491-z
23. Vernia P, Marinaro V, Argnani F, Di Camillo M, Caprilli R. Self-reported milk intolerance in irritable bowel syndrome: What should we believe? Clin Nutr 2004;23:996–1000. doi:10.1016/j.clnu.2003.12.005
24. Gupta D, Ghoshal UC, Misra A, Misra A, Choudhuri G, Singh K. Lactose intolerance in patients with irritable bowel syndrome from northern India: A case–control study. J Gastroenterol Hepatol 2007;22:2261–2265. doi:10.1111/j.1440-1746.2007.04986.x
25. Yang J, Deng Y, Chu H, et al. Prevalence and Presentation of Lactose Intolerance and Effects on Dairy Product Intake in Healthy Subjects and Patients With Irritable Bowel Syndrome. Clin Gastroenterol Hepatol 2013;11:262-268.e1. doi:10.1016/j.cgh.2012.11.034
26. Xiong L, Wang Y, Gong X, Chen M. Prevalence of lactose intolerance in patients with diarrhea-predominant irritable bowel syndrome: Data from a tertiary center in southern China. J Health Popul Nutr 2017;36:38. doi:10.1186/s41043-017-0113-1
27. Bouchoucha M, Fysekidis M, Rompteaux P, Raynaud JJ, Sabate JM, Benamouzig R. Lactose Sensitivity and Lactose Malabsorption: The 2 Faces of Lactose Intolerance. J Neurogastroenterol Motil 2021;27:257–264. doi:10.5056/jnm20094
28. Varjú P, Gede N, Szakács Z, et al. Lactose intolerance but not lactose maldigestion is more frequent in patients with irritable bowel syndrome than in healthy controls: A meta-analysis. Neurogastroenterol Motil 2019;31:e13527. doi:10.1111/nmo.13527
29. Lapides RA, Savaiano DA. Gender, Age, Race and Lactose Intolerance: Is There Evidence to Support a Differential Symptom Response? A Scoping Review. Nutrients 2018;10:1956. doi:10.3390/nu10121956
30. Mysore Saiprasad S, Moreno OG, Savaiano DA. A Narrative Review of Human Clinical Trials to Improve Lactose Digestion and Tolerance by Feeding Bifidobacteria or Galacto-Oligosacharides. Nutrients 2023;15:3559. doi:10.3390/nu15163559
31. Pei R, Martin DA, DiMarco DM, Bolling BW. Evidence for the effects of yogurt on gut health and obesity. Crit Rev Food Sci Nutr 2017;57:1569–1583. doi:10.1080/10408398.2014.883356
32. Suarez FL, Savaiano D, Arbisi P, Levitt MD. Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. Am J Clin Nutr 1997;65:1502–1506. doi:10.1093/ajcn/65.5.1502
33. Savaiano DA, Boushey CJ, McCabe GP. Lactose Intolerance Symptoms Assessed by Meta-Analysis: A Grain of Truth That Leads to Exaggeration. J Nutr 2006;136:1107–1113. doi:10.1093/jn/136.4.1107
34. Di Stefano M, Bergonzi M, Miceli E, Klersy C, Pagani E, Corazza GR. In irritable bowel syndrome, postprandial abdominal distention is associated with a reduction of intestinal tone. Neurogastroenterol Motil 2017;29(10):1-8. doi:10.1111/nmo.13098
35. Gargano D, Appanna R, Santonicola A, et al. Food Allergy and Intolerance: A Narrative Review on Nutritional Concerns. Nutrients 2021;13:1638. doi:10.3390/nu13051638
36. Spiller R. Impact of Diet on Symptoms of the Irritable Bowel Syndrome. Nutrients 2021;13:575. doi:10.3390/nu13020575