


Lactose intolerance but not lactose maldigestion is more frequent in patients with irritable bowel syndrome than in healthy controls: A meta-analysis

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Abstract

Background and Purpose: Irritable bowel syndrome (IBS) affects 10%-20% of the adult population and is characterized by abdominal symptoms without relevant organic disease. There are numerous clinical trials available investigating the relationship between IBS, lactose maldigestion (LM), and lactose intolerance (LI), but there have been no meta-analyses on this topic yet. We aimed to assess the prevalence of LM, objective and subjective (self-reported) LI in IBS patients compared to healthy controls (HC) without IBS.

Methods: A systematic literature search was conducted up to 24 April 2018 in PubMed, Embase, and Cochrane Library. Adult IBS patients had to be diagnosed according to the Rome criteria or other well-defined criteria system. We enrolled controlled studies including healthy adult participants without IBS, as control group. Odds ratios with 95% confidence intervals were calculated.

Key Results: Altogether 14 articles were suitable for statistical analyses. IBS patients reported themselves significantly more frequently lactose intolerant than HCs (odds ratio [OR] = 3.499; 95% confidence interval [CI] = 1.622-7.551). Generally, there was no significant difference in the prevalence of LM based on ingested lactose dose

Abbreviations: CI, confidence interval; CMA, Comprehensive Meta-Analysis Software; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; HC, healthy control; IBS, irritable bowel syndrome; IBS-D/C/M/A/U, irritable bowel syndrome diarrheal/constipation/mixed/alternating/unclassified form; IQR, interquartile range; LBT, lactose breath test; LI, lactose intolerance; LM, lactose maldigestion; LTT, lactose tolerance test; MRI, magnetic resonance imaging; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PICO, Participants, Intervention, Comparison, Outcomes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD, standard deviation; VAS, Visual Analog Scale.

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(OR = 1.122; 95% CI = 0.929-1.356) and test type (OR = 1.156; 95% CI = 0.985-1.356). However, significantly more IBS patients had objective LI (OR = 2.521; 95% CI = 1.280-4.965).

Conclusions and Inferences: Lactose intolerance, but not LM is more frequent among patients with IBS compared to HCs. According to our results, IBS among other functional bowel disorders is a possible contributing factor of LI in people with LM.

KEYWORDS

irritable bowel syndrome, lactose intolerance, lactose maldigestion

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most frequently diagnosed disorders in gastroenterology, which can be defined by the Rome IV criteria system.¹⁻³ It is characterized by abdominal pain related to defecation, and associated with a change in stool frequency or consistency (diarrhea, constipation, or a combination of these), without any organic disease or pathological abnormality of the gut-wall.⁴ Four subtypes of IBS can be separated: diarrheal (IBS-D), constipation (IBS-C), mixed or alternating (IBS-M/A) and unclassified (IBS-U) form.^{5,6} IBS can lead to significant quality of life impairment, decreased work productivity and an increase of health care and social costs.⁷⁻¹⁰ The prevalence of IBS is high in Western countries, affecting 10%-20% of the adult population.¹¹⁻¹³ Its pathogenesis remains unknown, but numerous factors may contribute to its development.^{3,14-16} Treatment is often multimodal, comprising of non-pharmacological and pharmacological methods. A novel effective treatment option is a low-FODMAP diet (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols), which suggests that certain food types, containing disaccharides like lactose, can trigger symptoms of patients with IBS.¹⁷⁻¹⁹

Lactose intolerance (LI) is a condition characterized by clinical symptoms after ingestion of lactose-containing products, caused by lactose maldigestion (LM).²⁰ The most common cause of LM is primary (adult-type) hypolactasia.³ LI affects 25% of the Caucasian population. Males and females are equally affected.^{21,22} Because of lactase deficiency, lactose can reach the large intestine where it is fermented by colonic bacteria. Short-chain fatty acids, gases (H₂, CO₂ and CH₄) and other products will be produced by the fermentation which can cause luminal distension and lead to different gastrointestinal symptoms. The most common complaints are abdominal pain and discomfort, bloating, flatulence, and diarrhea, similarly as in IBS.^{20,23-25} Due to the potential pathogenetic factors of IBS (altered gastrointestinal motility, changes of gut microbiome, visceral hypersensitivity, anxiety, etc), food intolerances, such as LI, are more frequent in this disease, however, the prevalence of LM does not differ compared with the healthy population. More IBS patients have symptoms at lower lactose doses and their symptoms are more severe. Moreover, many IBS patients think that their abdominal symptoms are related to lactose intake, even though no objective tests

Key Points

- The connection between IBS and lactose intolerance is not clearly described yet, therefore we performed meta-analysis to explore this association.
- We proved that lactose intolerance is more common in IBS, however, the frequency of lactose maldigestion is almost the same compared to healthy people.
- This suggests that IBS is a possible contributing factor in lactose intolerance among lactose maldigesters.

of LM were carried out.²⁶⁻³⁰ The available diagnostic methods for diagnosing LM or LI are based on several approaches, including lactose breath test (LBT), lactose tolerance test (LTT), genetic test and assessment of lactase activity in jejunal biopsy specimens.³ The restriction of lactose intake or the replacement of the lactase enzyme can alleviate these symptoms.^{3,21}

There are numerous clinical trials investigating the connection between IBS, LM, and LI, but to our best knowledge no meta-analyses have been performed up to this day.

Given the uncertain connection between IBS and lactose consumption-related disorders, we performed a systematic literature search and meta-analysis in this important topic with the aim to assess the prevalence of LM, objective and subjective LI in IBS patients compared to healthy controls (HC).

2 | MATERIALS AND METHODS

Our work was planned and conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 Statement (Table S1).

2.1 | Searching strategy

Our systematic literature search was based on the PICO format: Participants: subjects who underwent any form of LM or LI assessment; Intervention: IBS patients; Comparison: healthy controls;

Outcomes: prevalence of LM, subjective/objective LI. It was conducted by two independent reviewers (JC and PV) to find all relevant articles on the prevalence of LM, subjective and objective LI in IBS compared to HCs, up to 24 April 2018 (first search: 20 June 2017). The search covered three major databases (PubMed, Embase, and the Cochrane Library) with the terms “(‘irritable bowel syndrome’ OR ‘IBS’) AND (‘lactose intolerance’ OR ‘lactose maldigestion’ OR ‘lactose malabsorption’).” The reference lists of the relevant articles were hand searched and all appropriate records identified were included in the screening process. After this search process, language (only English) and species (only humans) filters were used. Duplicates were removed with EndNote X4 and manually, and then title and abstract screening was performed by the two reviewers to identify potentially eligible articles. Disagreements were resolved by consensus.

2.2 | Eligibility criteria

In our meta-analysis, we included all studies investigating the connection between IBS, lactose consumption-related symptoms, and maldigestion in comparison with HC group. Retrospective studies were also included. The length of follow-up was not a reason for either inclusion or exclusion. Only articles written in English and those examining the effect of lactose ingestion in human IBS patients were included in this study. Short conference abstracts or papers not available in full-text format were excluded. By definition, adult IBS patients (17 years or above) had to be diagnosed according to the Rome or, in articles that were not recently published, according to any other well-defined criteria system. Articles without clear definitions of IBS, or in which small intestinal bacterial overgrowth or any other organic diseases (inflammatory bowel disease, celiac disease, etc) were reported or suspected in the background, were excluded from the analysis. We enrolled controlled studies which included healthy adult participants (without organic disease) who did not fulfill IBS criteria, as a control group. Only articles reporting data about the prevalence of LM and/or subjective/objective LI in IBS and HC group were analyzed statistically.

2.3 | Quality assessment of the individual studies

The quality and the biases of the included studies were analyzed with the Newcastle-Ottawa Scale (NOS) for case-control studies.³¹ Two authors (IMC, PV) independently assessed the risk of bias in each paper included in the statistical analysis. Disagreements were resolved by consensus. If the discussion did not result in consensus, a third author was consulted (PH). The NOS for case-control studies contains eight items covering three main domains (selection, comparability and exposure). A study can be awarded a maximum of one star for each numbered item; on the contrary, a maximum of two stars can be given for comparability. Each item was rated as “high risk” (zero stars), “low risk” (one star) or “unclear risk” (zero stars) corresponding to the definitions.

2.4 | Data extraction

At the end of the screening process, relevant data were independently extracted from studies by two independent reviewers (JC and PV). These included: prevalence of LM and LI (subjective or objective) as the outcome parameters, first author, year of publication and country of origin, study design, basic characteristics of the study population (age, percentage of females and IBS subtypes, size of the study groups), diagnostic criteria for IBS, diagnostic methods, thresholds and lactose dose used to diagnose maldigestion. Data for the risk of bias (NOS) assessment were collected as well. Extracted data were validated by five co-authors (ZsSz; DP; MB; ÁV; JT).

2.5 | Outcome measure

The prevalence of LM, subjective and objective LI were the main outcome parameters in our analysis. LM can be diagnosed through different ways,²¹ the non-invasive and inexpensive LBT and LTT being the most common methods. The sensitivity and specificity of these tests depends on the lactose dose, but they are relatively high (78% and 93%).³² Before (baseline) and after the ingestion of a given amount of lactose, breath and blood samples are collected at different time points for a period of time and end-alveolar H₂ and blood glucose concentrations are measured. A certain rise of H₂ (or additionally methane) and/or no rise of blood glucose (or additionally galactose) above the baseline levels are considered diagnostic for lactose maldigestion. The amount of ingested lactose and the diagnostic thresholds were different in the studies. Testing of lactase activity in mucosal biopsy samples from duodenum or jejunum is the gold standard method in the diagnosis of LM, but due to the invasiveness, high costs and patchy expression of the enzyme it is performed less frequently, compared to the tests mentioned above. The availability of genetic testing of the genes associated with lactase non-persistence (C/T_13910 with CC genotype; G/A_22018 with GG genotype) is variable, and its costs are relatively high.²¹

Participants with LM who had abdominal symptoms during or shortly after lactose test were defined as objectively lactose intolerant. Participants reporting before any tests, that their symptoms can be in connection with ingestion of lactose-containing products, were defined as subjectively lactose intolerant.

2.6 | Statistical analysis

Pooled odds ratios (OR) were calculated with 95% confidence intervals (CI). Random effects and fixed model were applied at all of analyses with DerSimonian-Laird³³ estimation. Statistical heterogeneity was analyzed using the I^2 and the chi-square test to gain probability-values; $P < 0.1$ was defined to indicate significant heterogeneity.³⁴ Subgroups of test type (LBT, LTT, lactase activity, and genetic test) and lactose dosages (10-18 g, 20-25 g, and 40-50 g) were created in the analysis on the outcomes. Statistical analyses were performed using the Comprehensive Meta-Analysis Software (CMA, Biostat, NJ, USA). Forest plots were used to present the results of

the meta-analyses. To check for publication bias, the visual inspection of funnel plots and Eggers' tests were performed.

3 | RESULTS

3.1 | Search results

Using the terms mentioned above, we found 647 articles in the three databases for evaluation, 213 in PubMed, 413 in Embase and 21 in Cochrane Library. We also examined 14 further articles from the reference lists of relevant articles, so 661 articles were found in total. After using the language (only English) and species (only humans) filters in Embase, PubMed and the Cochrane Library, 520 of 647 studies were further assessed and none of the articles from the reference lists were excluded. After removing duplicates, title and abstract screening, 89 articles reporting on lactose consumption-related disorders in IBS and eligible for further evaluation were found. The detailed screening of the full-text papers identified 16 articles for further assessment, of which two were not suitable for statistical analysis. Altogether 14 case-control studies met the inclusion criteria and remained for quantitative analysis.^{26,27,35-46} The flow chart of the systematic literature search was based on the PRISMA 2009 guideline and is detailed on Figure 1. At the time of the literature search, we found no eligible paper that used the most recent diagnostic criteria (Rome IV) for IBS. The

basic characteristics of the articles and the raw data are summarized in Tables 1 and S2. The proportion of each IBS subtype and the used lactose doses, diagnostic methods for LM and thresholds in the studies included in the meta-analysis are detailed in Table 2. A quality assessment (NOS) of the articles is summarized in Tables 3 and S3.

3.2 | Lactose maldigestion and IBS

In 13 of the 14 articles, LM was objectively tested with LBT, LTT or genetic testing. There were not enough controlled studies with lactase activity measurement to carry out a correct statistical analysis. In one of the included case-control studies, only subjective LI was assessed.⁴²

Based on the ingested lactose dose used in the different studies three subgroups were made: 10-18 g; 20-25 g; 40-50 g (Figure 2). Overall there was no significant difference in the prevalence of LM between IBS and HC groups (OR = 1.122; 95% CI: 0.929-1.356; $P = 0.232$). The I^2 test showed no significant heterogeneity ($I^2 = 0.000\%$; $P = 0.479$). We did not find significant difference either between ($P = 0.121$), or within the subgroups: (1) OR = 1.420, 95% CI: 0.873-2.309, $P = 0.158$ ($I^2 = 0.000\%$; $P = 0.810$); (2) OR = 0.926, 95% CI: 0.711-1.206, $P = 0.568$ ($I^2 = 11.037\%$; $P = 0.338$); (3) OR = 1.356, 95% CI: 0.977-1.882, $P = 0.068$ ($I^2 = 0.000\%$; $P = 0.651$). There was no significant heterogeneity within the subgroups.

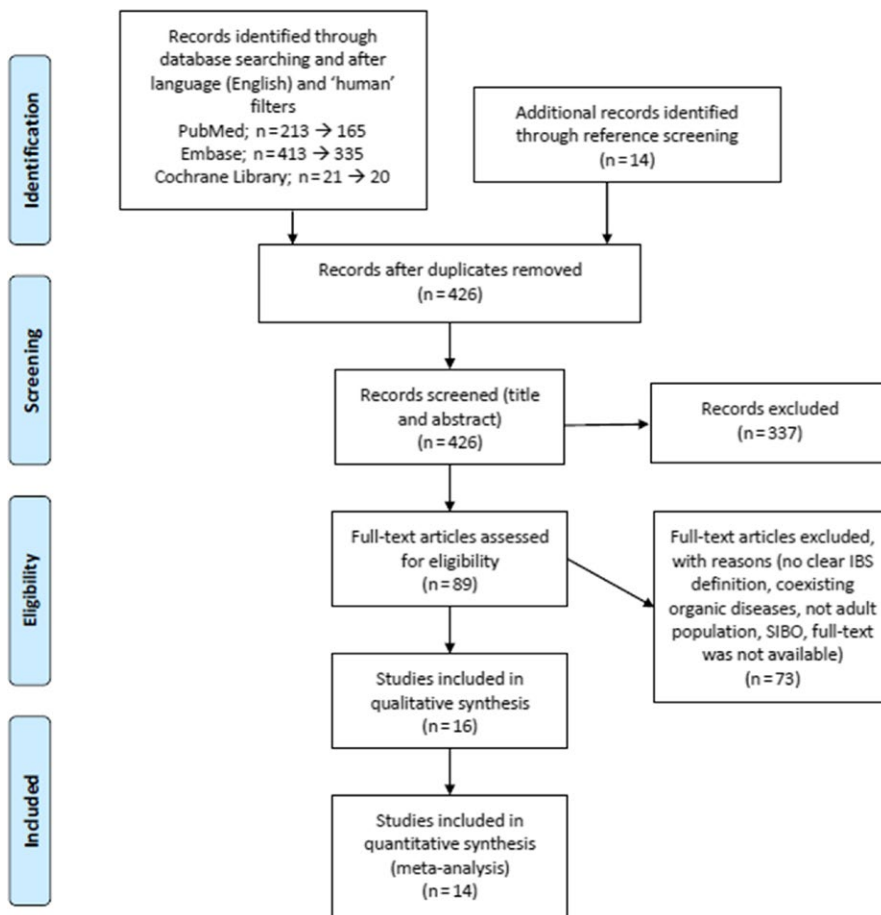


FIGURE 1 PRISMA-flowchart of the systematic literature search. IBS: irritable bowel syndrome; SIBO: small intestinal bacterial overgrowth

TABLE 1 Characteristics of the studies included in the statistical analyses

First author, year, reference number	Country	Study design	IBS diagnostic criteria	Number of participants (IBS/HC)	Age (IBS/HC), years	Percentage of females (IBS/HC)
Bianchi Porro et al. (1983) ³⁵	Italy	Case-control	Unspecific abdominal complaint (primarily colicky abdominal pain and/or intermittent diarrhea or dyspepsia) for at least 1 year without any organic disease	77/40	Group 1: mean 42.2 (range: 19-53); group 2: mean 41.2 (range: 18-54)/mean 35.05 (range: 18-55)	51.9/52.5
Gwee et al. (1996) ³⁶	UK	Case-control	Rome criteria	22/53	Median 34 (IQR: 23.5-51)/median 36 (IQR: 27-52)	77/36
Vesa et al. (1998) ³⁷	Finland	Case-control	Rome criteria	63/364	Mean 51 ± 9 SD/mean 50 ± 9 SD	68/50
Goldstein et al. (2000) ³⁸	Israel	Case-control	Rome criteria	94/145	Women: mean 44.4 ± 17.5 SD; men: mean 42.7 ± 18.6 SD/women: mean 49.6 ± 18.9 SD men: mean 35.7 ± 15.7 SD	No data
Vernia et al. (2001) ²⁷	Italy	Case-control	Rome criteria	503/336	Women: mean 37.8 ± 13.9 SD men: mean 36.2 ± 13.9 SD / women: mean 36.1 ± 14.8 SD men: mean 32.1 ± 13.5 SD	66.7/65.1
Parry et al. (2002) ³⁹	UK	Case-control	Rome II	16/18	Mean 44.4 (range 25-76)	No data/55.5
Lanng et al. (2003) ⁴⁰	Denmark	Case-control	Kay and Jørgensen criteria: More than weekly experience of abdominal pain and distension and in addition either borborygmi or altering stool consistency	32/26	Mean 51.8/mean 52.8	75/53.8
Farup et al. (2004) ⁴¹	Norway	Case-control	Rome II	82/105	Mean 48.8/mean 46.3	68/78
Saberi-Firoozi et al. (2007) ⁴²	Iran	Case-control	Rome II	215/1763	Mean 49.9 ± 11.14 SD	64.2
Corlew-Roath et al. (2009) ⁴³	USA	Case-control	Rome III	66/55	All participants over 18 years	86/62
Yakoob et al. (2011) ⁴⁴	Pakistan	Case-control	Rome III	119 /115	Mean 35 ± 13 SD (range: 18-74)/mean 36 ± 15 SD (range: 18-80)	26.05/33.04
Kumar et al. (2012) ⁴⁵	India	Case-control	Rome III	150/252	Mean 36.7 ± 11.8 SD/mean 37.2 ± 11.5 SD	24/22
Yang et al. (2013) ²⁶	China	Case-control	Rome III	60/60	Mean 40.8 ± 11.7 SD/mean 40.8 ± 15.2 SD	51.6/48.3
Xiong et al. (2017) ⁴⁶	China	Case-control	Rome III	109/50	Mean 36.0 ± 12.2 SD/mean 34.8 ± 13.3 SD	47.7/48

HC, healthy control; IBS, irritable bowel syndrome; IQR, interquartile range; SD, standard deviation.

TABLE 2 The percentage of IBS subtypes and the diagnostic methods and thresholds used in the analyzed studies

First author, year, reference number	IBS subtypes (%)	Diagnostic method for LM	Amount of lactose (g)	Diagnostic threshold for LM
Bianchi Porro et al. (1983) ³⁵	No data	LBT, LTT, lactase activity (jejunal biopsy)	LBT: 50 LTT: 100	LBT: >20 ppm H ₂ rise LTT: <20 mg/100 mL rise of blood glucose lactase activity: ≤39 IU/g protein
Gwee et al. (1996) ³⁶	IBS-D: 86 IBS-C: 9 IBS-M/A: 5	LBT	50	No data
Vesa et al. (1998) ³⁷	No data	LTT	50	Blood glucose elevation <1.1 mmol/L (20 mg/100 mL) and maximal rise in blood galactose concentration ≤0.3 mmol/L (5 mg/100 mL)
Goldstein et al. (2000) ³⁸	No data	LBT	18	≥20 ppm rise of H ₂ or ≥5 ppm rise of CH ₄ over baseline value
Vernia et al. (2001) ²⁷	IBS-D: 24.8 IBS-C: 13.3 IBS-M/A: 17.1	LBT	0.5 g/kg body weight up to a maximum of 25 g	H ₂ peak exceeding 20 ppm over the baseline values
Parry et al. (2002) ³⁹	No data	LBT, LTT	50	A failure of plasma glucose to rise by more than 1.1 mmol/L from baseline. A rise in the breath hydrogen value above 20 ppm from baseline
Lannig et al. (2003) ⁴⁰	No data	LTT	50	Glucose level rise ≤1.3 mmol/L
Farup et al. (2004) ⁴¹	No data	LBT	25	Peak values of H ₂ breath excretion >20 ppm above the lowest preceding value, peak CH ₄ excretion >12 ppm above baseline, and/or combined H ₂ and CH ₄ increase >15 ppm were considered diagnostic
Saberi-Firoozi et al. (2007) ⁴²	No data	-	-	-
Corlew-Roath et al. (2009) ⁴³	No data	LBT	50	H ₂ , CH ₄ , and CO ₂ were tested (threshold: no data)
Yakoob et al. (2011) ⁴⁴	IBS-D: 100	LBT	50	H ₂ rise above baseline of 20 ppm
Kumar et al. (2012) ⁴⁵	IBS-D: 52 IBS-C: 35 IBS-M/A: 13	Genetic test	-	C/T_13910 (CC genotype)/G/A_22018 genetic variant (GG genotype)
Yang et al. (2013) ²⁶	IBS-D: 100	LBT, genetic test	10, 20, 40	≥20 ppm H ₂ rise above the baseline, C/T_13910 (CC genotype)
Xiong et al. (2014) ⁴⁶	IBS-D: 100	LBT	25	Peak hydrogen breath excretion of 20 ppm above the baseline level

IBS-D/C/M/A, irritable bowel syndrome-diarrheal/constipation/mixed/alternating subtype; LBT, lactose breath test; LM: lactose maldigestion; LTT, lactose tolerance test.

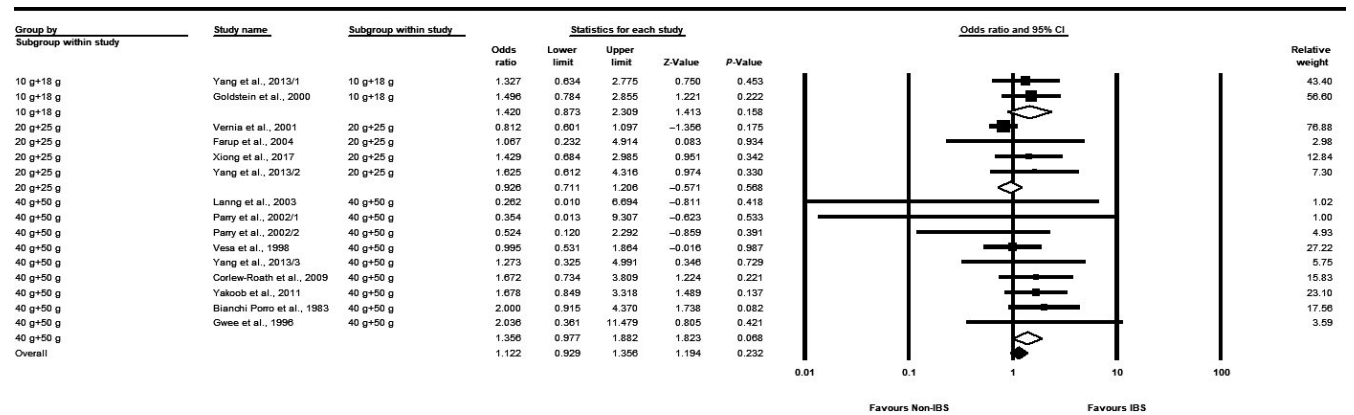
According to the test methods, three subgroups were made: (1) genetic test; (2) LBT and (3) LTT (Figure 3). Overall, there was no significant difference in the prevalence of LM between IBS patients and HCs (OR = 1.156; 95% CI: 0.985-1.356; $P = 0.077$) and the analyzed studies were homogeneous ($I^2 = 0.548\%$; $P = 0.590$). We did not find significant difference either between ($P = 0.548$) or within the subgroups: (1) OR = 1.243, 95% CI: 0.922-1.677, $P = 0.154$ ($I^2 = 0.000\%$; $P = 0.664$); (2) OR = 1.159, 95% CI: 0.948-1.416, $P = 0.150$ ($I^2 = 4.977\%$; $P = 0.396$); (3) OR = 0.868, 95% CI: 0.492-1.533, $P = 0.626$ ($I^2 = 0.000\%$; $P = 0.561$). There was no significant heterogeneity within the subgroups.

Based on the test type and ingested amount of lactose, four subgroups were made: (1) 20-25 g LBT; (2) 40-50 g LBT; (3) 40-50 g LTT and (4) 10-18 g LBT (Figure 4). Overall there was no significant difference between IBS and control groups in the prevalence of LM (OR = 1.122; 95% CI: 0.929-1.356; $P = 0.232$) and the analyzed studies were homogeneous ($I^2 = 0.000\%$; $P = 0.479$). LM was more frequent among IBS patients who underwent LBT with 40-50 g lactose (b) compared to HCs (OR = 1.692; 95% CI: 1.134-2.527; $P = 0.010$; $I^2 = 0.000\%$; $P = 0.938$). Between ($P = 0.051$) and within the other subgroups there was no significant difference: (1) OR = 0.926, 95% CI: 0.711-1.206, $P = 0.568$ ($I^2 = 11.037\%$; $P = 0.338$); (c) OR = 0.868,

TABLE 3 The quality and risk of bias assessment of the included studies according to Newcastle-Ottawa Scale for case-control studies³¹

First author, year, reference number	Selection				Comparability	Exposure			NOS summarized score
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	
Bianchi Porro et al. (1983) ³⁵	0	*	*	*	**	*	*	0	7/9
Gwee et al. (1996) ³⁶	0	*	0	0	*	*	*	0	4/9
Vesa et al. (1998) ³⁷	*	0	*	*	*	*	*	0	6/9
Goldstein et al. (2000) ³⁸	*	*	0	0	**	*	*	0	6/9
Vernia et al. (2001) ²⁷	*	*	*	*	0	*	*	0	6/9
Parry et al. (2002) ³⁹	*	*	0	*	*	*	*	0	6/9
Lanng et al. (2003) ⁴⁰	*	*	*	*	**	*	*	0	8/9
Farup et al. (2004) ⁴¹	*	*	*	*	**	*	*	0	8/9
Saberi-Firoozi et al. (2007) ⁴²	*	*	*	0	0	*	0	0	4/9
Corlew-Roath et al. (2009) ⁴³	*	*	0	0	0	*	*	0	4/9
Yakoob et al. (2011) ⁴⁴	*	*	0	*	**	*	*	*	8/9
Kumar et al. (2012) ⁴⁵	*	*	0	0	**	*	*	0	6/9
Yang et al. (2013) ²⁶	*	*	0	*	**	*	*	0	7/9
Xiong et al. (2017) ⁴⁶	*	*	*	*	**	*	*	*	9/9

The NOS consists of eight numbered items, divided into three main sections (selection, comparability, and exposure). Each numbered item can be rewarded with maximum one star; comparability can be awarded with two stars. The studies with maximum of nine stars representing the highest-quality trials with the lowest risk of bias. The detailed analysis of each study is represented in Table S3. NOS, Newcastle-Ottawa Scale.



Meta Analysis

FIGURE 2 The difference of LM between IBS and HCs, based on the ingested lactose dose (10-18 g, 20-25 g, 40-50 g). There was no significant difference either overall, or in the subgroups. HC, healthy controls; IBS, irritable bowel syndrome; LM, lactose maldigestion

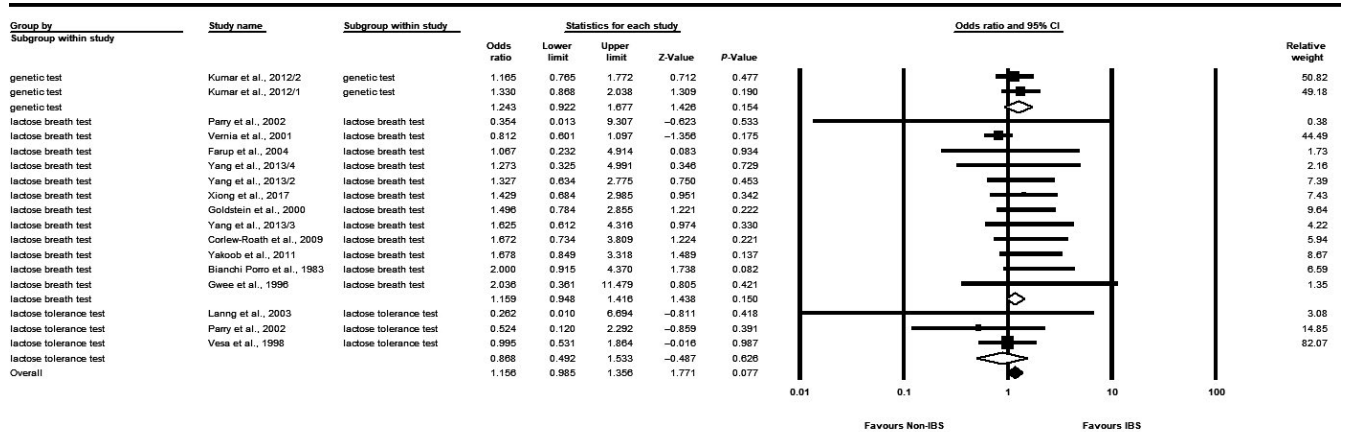
95% CI: 0.492-1.533, $P = 0.626$ ($I^2 = 0.000\%$; $P = 0.561$); (4) OR = 1.420, 95% CI: 0.873-2.309, $P = 0.158$ ($I^2 = 0.000\%$; $P = 0.479$). There was no significant heterogeneity within the subgroups.

3.3 | Lactose intolerance

Only four case-control studies published data about self-reported (subjective) LI.^{26,37,41,42} Our results (Figure 5) showed that subjective LI was more common in IBS compared to HCs, patients reported more often

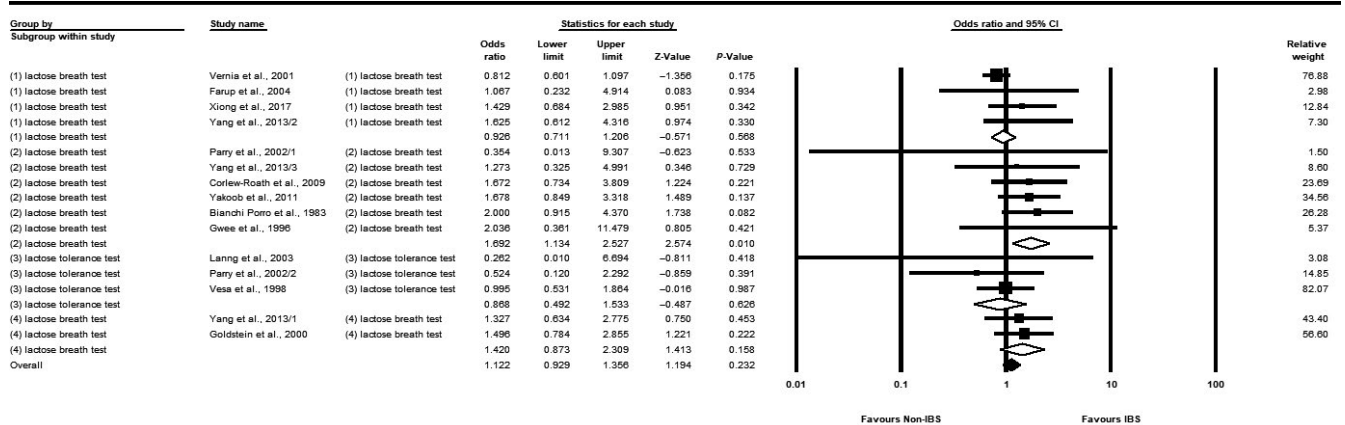
that their abdominal symptoms can be related to lactose-containing products (OR = 3.499; 95% CI: 1.622-7.551; $P = 0.001$). The examined population was significantly heterogeneous ($I^2 = 86.774\%$; $P = 0.000$).

There were three articles available reporting on objective LI (Figure 6).^{26,27,46} Significantly more maldigester IBS patients reported abdominal symptoms during or shortly after the diagnostic test compared to controls (OR = 2.521; 95% CI: 1.280-4.965; $P = 0.008$), but our result is limited by the heterogeneity of the analyzed population ($I^2 = 74.866\%$; $P = 0.003$).



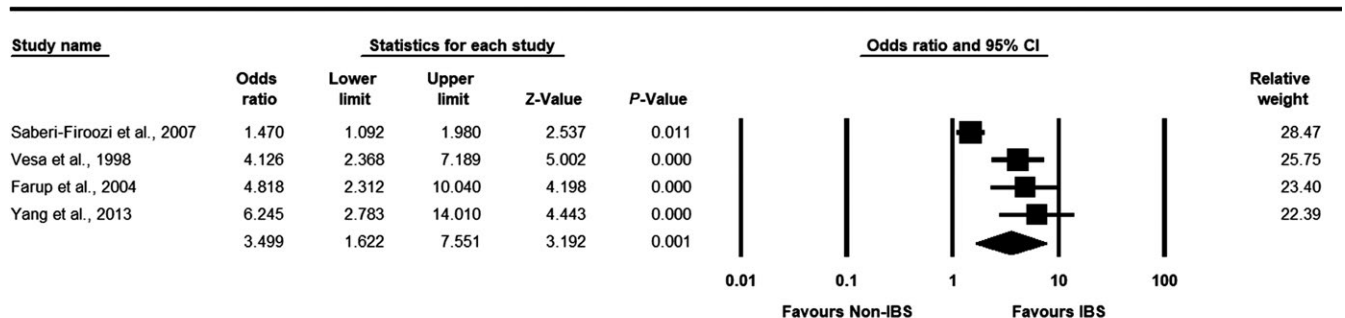
Meta Analysis

FIGURE 3 The difference of LM between IBS and HCs, based on the diagnostic method (LBT, LTT, genetic test). There was no significant difference either overall, or in the subgroups. HC, healthy controls; IBS, irritable bowel syndrome; LBT, lactose breath test; LM, lactose maldigestion; LTT, lactose tolerance test



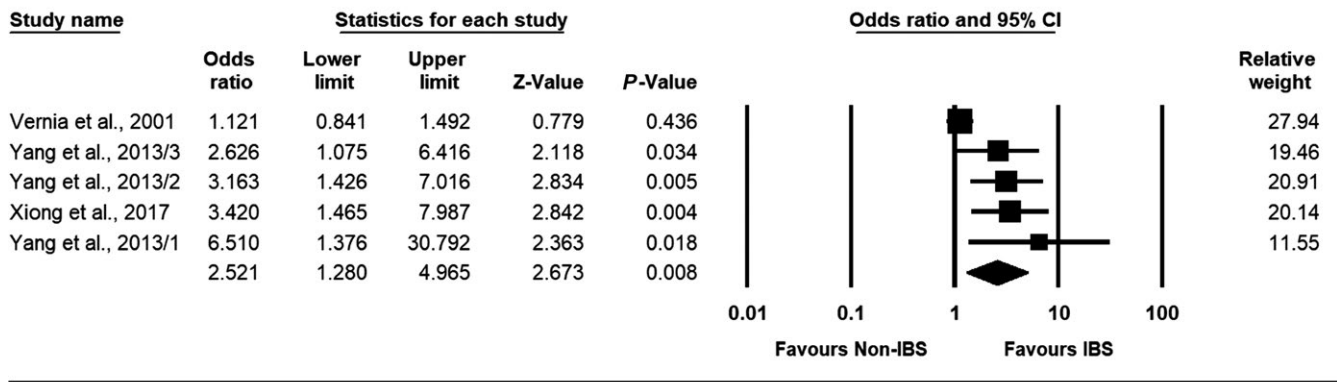
Meta Analysis

FIGURE 4 The difference of LM between IBS and HCs, based on the lactose dose and diagnostic method. LM was significantly more frequent in IBS only at the LBT with the highest lactose dose (40-50 g). HC, healthy controls; IBS, irritable bowel syndrome; LBT, lactose breath test; LM, lactose maldigestion



Meta Analysis

FIGURE 5 The difference of subjective (self-reported) LI between IBS and HCs. Subjective LI was significantly ($P = 0.001$) more frequent in IBS compared to the control group. HC, healthy controls; IBS, irritable bowel syndrome; LI, lactose intolerance



Meta Analysis

FIGURE 6 The difference of objective LI between IBS and HCs. Objective LI was significantly ($P = 0.008$) more frequent in IBS compared to the control group. HC, healthy controls; IBS, irritable bowel syndrome; LI, lactose intolerance

4 | DISCUSSION

A growing number of studies have shown that intolerance to lactose-containing products and other food types is more frequent among patients with IBS than among healthy subjects, but to our best knowledge, no meta-analysis investigated the association between these two conditions so far. Only two recent reviews by Borghini and Bayless et al.^{3,47} discuss the correlation between IBS and LI.

We carried out a systematic literature search and quantitative data (meta-) analysis on the topic. A pooled analysis of 14 case-control trials confirmed a significantly higher prevalence of subjective and objective LI, whereas nearly the same prevalence of LM in IBS patients compared to healthy participants. The underlying mechanism remains unknown, but common etiological factors like psychological (eg anxiety) and gastrointestinal dysfunctions (eg visceral hypersensitivity and altered gut transit) might play a role.²⁸⁻³⁰ The visceral hypersensitivity can also be in connection with altered gut microbiome. Gut microbiota of IBS patients is generally reduced and has lower diversity, compared to healthy controls.⁴⁸ It has been shown that potentially pathogenic bacteria (eg *Clostridium* spp, *Ruminococcus* spp, *Streptococcus* spp, *Enterobacteriaceae* members) are more concentrated in IBS patients than in controls.⁴⁹⁻⁵² A recent MRI (magnetic resonance imaging) study concluded that visceral hypersensitivity, rather than excessive gas production is responsible for carbohydrate associated symptoms in patients with IBS.⁵³ The hypersensitivity to colonic distension can be transferred to mice by fecal transplantation which highlights the role of microbiome.⁵⁴ Moreover, gut microbiota produces many neuroactive or neuromodulatory metabolites (histamine, serotonin, gamma-aminobutyric acid, brain derived neurotrophic factor, etc), which can potentially lead to peripheral or central neural sensitization.^{55,56}

Most studies have shown a beneficial effect of lactose-free or restricted diet in IBS.^{25,57,58} One reason might be that lactose belongs to FODMAPs, which are poorly absorbed carbohydrates leading to increased water content in the bowel based on the compounds'

osmotic effect and increased gas production by colonic bacterial flora, inducing symptoms in patients with IBS and numerous patients with functional gastrointestinal disorders. Based on these findings, a low-FODMAP diet could be beneficial in these patients.¹⁷⁻¹⁹

In the present study, the pooled sample size was large concerning the key question and the random effects and fixed model were used with the DerSimonian and Laird method³³ for analysis. Study data reflected no publication bias according to the analyses of LM status (Figures S1, S2 and S3), but showed significant bias (small study effect) based on heterogeneity in forest plots of subjective and objective LI (Figures S4 and S5).

We evaluated the quality of the studies included in the meta-analysis with the NOS for case-control studies, which showed satisfactory scores of the trials with low or medium risk of bias (Tables 3 and S3).

The strength of our study is that standardized, well-defined, rigorous outcome measures were used to assess the role of lactose consumption-related disorders in IBS patients, and a sufficient number of articles were found to carry out a detailed statistical analysis. Only full-text papers were enrolled, where IBS patients with appropriate control groups were present. According to our results, more IBS patients reported themselves lactose intolerant before any objective tests compared to HCs, which can be highlighted with objective measures: significantly more maldigester IBS patients reported abdominal symptoms during or shortly after the diagnostic test (objective LI). However, except for the LBT with the highest lactose doses (40-50 g), the prevalence of LM was similar in the study groups. Our meta-analysis is the first to provide evidence for the connection between IBS and LI and our former¹⁸ data suggest that a lactose-free or lactose-restricted diet (low-FODMAP) in the treatment of IBS could improve the therapeutic effect on IBS symptoms and might decrease health care-related and societal costs.

There are some limitations of our study. Firstly, we focused on the prevalence of LM and subjective/objective LI, and due to the lack of detailed, uniform, controlled, published data, we could not

perform a statistical analysis of individual symptoms. A uniform, consensus-based, well-comparable measurement of symptom severity, for example visual analog scale (VAS) is suggested for use in future studies. Because of the same reasons, we could not analyze the role of lactose-restricted diet or lactase replacement in this patient group; therefore, a network meta-analysis could be a useful future perspective to establish which treatment is better in IBS. Secondly, because of the lack of data in the different IBS subtypes, it is not clear which subgroup is mostly affected by LI. Moreover, the diagnostic criteria for IBS and the diagnostic thresholds of LBT and LTT were different in some studies which could influence the results. The sensitivity and specificity of these non-invasive tests are relatively high; however, false positive or negative results could have an effect on our findings. It should be taken into account that similar activity of lactase in two persons might result in different LBT results due to the different activity and composition of the intestinal microbiota and the lactase non-persistence allele is not always associated with LM.²¹ Another difficulty is that it is hard to identify the food, responsible for the symptoms. The correlation between self-reported and objective LI increases with the ingested lactose dose.²⁶ Finally, we found significant heterogeneity in the analysis of the subjective and objective LI. We could not perform subgroup analysis with different amount of lactose in LI, however, it can influence the frequency and severity of the abdominal symptoms and therefore the prevalence of objective LI, as presented by Yang et al.²⁶

More trials with standardized parameters are necessary in the future to provide the best quality of evidence regarding the correlation between IBS and LI. Only patients fulfilling the most recent diagnostic criteria for IBS (Rome IV) should be included in such studies. Outcomes should be reported for each IBS subtypes. Uniform outcome measures (eg VAS) regarding abdominal symptoms should be used to make the different studies scientifically comparable. More randomized controlled trials are needed to provide evidence about the role of lactose-free or restricted diet in IBS compared to placebo or lactase replacement. In these studies, a more accurate IBS-Symptom Severity Score (IBS-SSS) should be used in each IBS subtype, which measures not only the severity of the main symptoms, but also the quality of life. Clinical trials with different lactose doses are also suggested to test the role of IBS in LI among lactose maldigesters. Yao et al.⁵⁹ discuss the crucial points and difficulties of designing clinical trials in dietary interventions in patients with functional gastrointestinal disorders.

5 | CONCLUSION

This meta-analysis is the first to confirm that subjective and objective LI are more common in IBS patients compared to the healthy population, but LM has the same prevalence. Based on these findings and literature data, IBS can be a contributing factor of LI among people with LM. Further studies are needed to determine whether a confirmed diagnosis of IBS is an etiological factor in determining whether LM patients present with LI.

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CONFLICT OF INTEREST

No competing interests declared.

AUTHOR CONTRIBUTION

PV performed the systematic literature search, extracted data, conducted bias analysis, interpreted the results and drafted the manuscript; NG performed the statistical analysis; ZsSz, DP, MB, ÁV, and JT validated the extracted data, critically revised the manuscript for important intellectual content and approved the submitted draft; PH contributed at the bias assessment, critically revised the manuscript for important intellectual content and approved the submitted draft; IMC performed the bias assessment, critically revised the manuscript for important intellectual content and approved the submitted draft; AF, ZSz, DC, AG, ZR supervised, critically revised the manuscript for important intellectual content and approved the submitted draft; JC studied the concept and design, performed the literature search, contributed in data extraction, critically revised the manuscript for important intellectual content and approved the submitted draft. He is the guarantor for this paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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