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Article *in* QJM: monthly journal of the Association of Physicians · August 2010

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Q J Med 2010; **103**:555–572
doi:10.1093/qjmed/hcq082 Advance Access Publication 3 June 2010

Review

QJM

Lactose malabsorption and intolerance: a systematic review on the diagnostic value of gastrointestinal symptoms and self-reported milk intolerance

P. JELLEMA[1], F.G. SCHELLEVIS[1,2], D.A.W.M. VAN DER WINDT[1,3], C.M.F. KNEEPKENS[4] and H.E. VAN DER HORST[1]

[1]*Department of General Practice, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam,* [2]*Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands,* [3]*The Arthritis Research Campaign National Centre for Primary Care, Keele University, Keele, Staffordshire, UK and* [4]*Department of Pediatric Gastroenterology, VU University Medical Centre, Amsterdam, The Netherlands*

Address correspondence to Prof. François G. Schellevis, Department of General Practice, EMGO Institute for Health and Care research, VU University Medical Centre and NIVEL (Netherlands Institute for Health Services Research), Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. email: f.schellevis@vumc.nl

Summary

Background: When lactose malabsorption gives rise to symptoms, the result is called 'lactose intolerance'. Although lactose intolerance is often bothersome for patients, once recognized it may be managed by simple dietary adjustments. However, diagnosing lactose intolerance is not straightforward, especially in primary care.

Aim: To summarize available evidence on the diagnostic performance of gastrointestinal symptoms and self-reported milk (lactose) intolerance in primary care, and the relationship between lactose malabsorption and intolerance.

Data sources: PubMed, EMBASE and reference screening.

Study selection: Studies were selected if the design was a primary diagnostic study; the patients were adults consulting because of non-acute abdominal symptoms; the diagnostic test included gastrointestinal symptoms and/or self-reported milk intolerance. A total of 26 primary diagnostic studies were included in the review.

Data extraction: Quality assessment and data extraction were performed by two reviewers independently. They adhered to the most recent guidelines for conducting a diagnostic review as described in the Cochrane Diagnostic Reviewers' Handbook.

Results: The diagnostic performance of diarrhea, abdominal pain, bloating, flatulence and self-reported milk intolerance was highly variable. A non-Caucasian ethnic origin was associated with the presence of lactose malabsorption. Both lactose malabsorbers and lactose absorbers reported symptoms during the lactose hydrogen breath test.

Conclusions: Our review shows that high-quality studies on the diagnosis of lactose malabsorption and intolerance in primary care are urgently needed. An important prerequisite would be to clearly define the concept of lactose intolerance, as well as how it should be assessed.

Background

Lactose malabsorption is the most common type of carbohydrate malabsorption and is caused by low lactase levels.[1] Lactase activity is highest at birth and declines after weaning. The age at which this decline starts and the proportion of the adult population with lactase levels low enough to be considered having 'hypolactasia' are both strongly related to ethnicity, with highest rates of lactose malabsorption in Asian populations, Native Americans and African Americans (60–100%) and lowest rates in people of northern European origin and the US white population (2–22%).[2] When lactose malabsorption gives rise to symptoms, this is called 'lactose intolerance'. Although lactose intolerance is often bothersome for patients, once recognized it may be managed by simple dietary adjustments.

Diagnosing lactose intolerance is not straightforward. First, symptoms consistent with lactose intolerance (abdominal pain, bloating, flatulence and diarrhea) are common and may have many other causes.[3–6] This is especially true for the primary care setting in many countries, due to its unselected population (i.e. absence of a referral filter). Irritable bowel syndrome, dyspepsia, inflammatory bowel disease, celiac disease and even malignancies are all part of the differential diagnosis.[7] Secondly, evidence on the diagnostic value of the symptoms consistent with lactose intolerance has not been systematically been reviewed yet. This evidence is highly needed, especially for primary care as signs and symptoms are the primary care physician's main diagnostic tools. Thirdly, the diagnostic value of self-reported milk intolerance is still a matter of debate; while on the one hand many more people seem to attribute their symptoms to lactose intake than objective testing is able to confirm,[3] on the other hand many patients fail to recognize an actual association.[7] Restriction of dietary lactose intake on the basis of self-reported milk intolerance without having been tested on lactose malabsorption may be unnecessary, if not detrimental to health.[8] Lastly, the lactose hydrogen breath test (LHBT) is currently considered to be the diagnostic method of choice, but actually identifies lactose malabsorption rather than lactose intolerance.[5] As both patients with a positive and patients with a negative LHBT result may report symptoms during a LHBT, the discrimination of lactose malabsorption from lactose intolerance is complex, as has also been demonstrated in a recently published study.[9]

The aim of this review is to summarize all available evidence on the diagnostic value of gastrointestinal (GI) symptoms and self-reported milk intolerance. Additionally, we studied the relationship between lactose malabsorption and intolerance by analyzing the association between LHBT results and the presence of symptoms after lactose ingestion. In this review the setting of interest is primary care.

Methods

Data sources and searches

We searched PubMed and Embase for all eligible diagnostic studies (till November 2008). The search strategy used MeSH/EMTREE terms and free text words, and included sub-searches related to the index test, target condition, study population and publication type. A methodological filter for the identification of diagnostic studies was added to increase the specificity of the search. The full search strategies can be obtained from the corresponding author on request.

Reference lists of all retrieved primary diagnostic studies were checked for additional relevant studies. Additionally, references were checked of relevant reviews, meta-analyses, guidelines and editorials.

Study selection

Two authors (P.J. and F.S.) independently applied the pre-defined selection criteria (see below). P.J. checked all titles and abstracts, while F.S. checked eligibility of those assessed by P.J. as (possibly) relevant, as well as a random selection of citations assessed as not relevant. Full publications were retrieved for studies that seemed relevant and those for which relevance was still unclear. Disagreements were resolved by consensus. A third reviewer was consulted in cases of persisting disagreement.

Participants, setting and study design

We considered primary diagnostic studies relevant if the study population consisted of adults (≥18 years) experiencing non-acute abdominal symptoms. Studies solely including persons with self-reported milk intolerance were excluded.

We intended to include only primary care studies, but due to the low number we decided to also include studies including patients visiting an outpatient GI clinic, as well as studies in which symptomatic adults had been recruited after population-based screening.

We included primary diagnostic studies with a cohort design, as well as case–control designs in which controls were diagnosed with functional bowel disorders or irritable bowel syndrome (IBS), as these may reflect an adequate representation of

a primary care population with non-acute abdominal pain. For the same reason we included cohort studies in which all patients had been diagnosed with a functional bowel disorder or IBS, or case–control studies comparing IBS patients with healthy controls that presented diagnostic data for the IBS group separately. We excluded cohort studies in which all participants had an established organic diagnosis (e.g. inflammatory bowel disease), as well as other case–control study designs, case reports, editorials and papers written in other languages than English, Dutch, German or French. Authors of studies that did not present enough data to extract a diagnostic two-by-two table were contacted for additional data.

Reference test and target condition

Only studies using a LHBT as reference test were included. An LHBT is considered to be the most reliable, non-invasive, economical technique.[6] The formerly usual test dose was 50 g; however, a 25 g dose is usual in clinical practice and has recently been confirmed as the recommended dosage.[7,10] Studies using duodenal biopsy or a lactose tolerance test with blood glucose measurements as the only reference test were excluded. Duodenal biopsy with assessment of lactase activity is considered to be a less rigid test than the LHBT, as disaccharidase activity in a small bowel biopsy specimen may not necessarily reflect the activity in the small bowel as a whole.[6] The lactose tolerance test with blood glucose measurements preceded the LHBT and is still sometimes used, but it is now recognized to yield an unacceptable number of both false-positive and false-negative test results.[1] We defined a positive LHBT result as lactose malabsorption, and a positive LHBT result plus accompanying clinical symptoms after the lactose load as lactose intolerance.

Index tests

Only studies on tests that can be carried out or are accessible in primary care were included, specifically: (i) presenting symptoms (before conducting the LHBT); (ii) self-reported milk intolerance; (iii) symptoms reported after lactose load (i.e. during the LHBT or immediately thereafter).

Data extraction and quality assessment

Data extraction and quality assessment were pre-tested using two studies not included in the review. Two authors (P.J., H.v.d.H.) used, independently from each other, a standardized form to extract data on setting and design; study population; test characteristics; and test results. Test results for healthy controls were not extracted. Quality was assessed by using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool,[1,11] which is recommended by the Cochrane Diagnostic Reviewers' Handbook.[12] This modified version consists of 11 items on methodological characteristics that have the potential to introduce bias (Table 1). Items were scored as 'positive' (i.e. no bias), 'negative' (i.e. potential bias) or 'unclear'. Inter-observer agreement was quantified by computing the percentage agreement per item; disagreements were resolved by consensus. We did not apply weights to the QUADAS items, nor used a summary quality score in the analysis. Instead, we decided, *a priori*, to explore whether scores on the following quality items explained variation in diagnostic performance: item 1 (validity of study sample), item 2 (blinded interpretation of results of index test) and item 5 (reference standard is likely to classify the target condition correctly).

Data synthesis and analysis

We present diagnostic two-by-two tables and diagnostic performance measures per research question. For the calculation of diagnostic performance measures and corresponding 95% confidence intervals (CIs) per study, we used MetaDiSc statistical software.[12,13] When appropriate, we additionally present the results of pairs of sensitivity and 1-specificity in a scatterplot. When four or more studies on a specific index test showed sufficient clinical and statistical homogeneity we used bivariate analyses to calculate pooled estimates of sensitivity and specificity and 95% CIs for the summary estimates.[14,15] Bivariate analyses take into account both within- and between-study variability, and perform better than SROC regression models derived with the Moses and Littenberg method, which departs from a fixed effects model.[16] We refrained from pooling when there was considerable statistical heterogeneity.

Investigations of heterogeneity

Factors that may contribute to variation in diagnostic performance across studies (heterogeneity) included differences in (i) setting of care: primary care vs. other; (ii) low vs. prevalence of lactose malabsorption using 30% as cut-off; (iii) exclusion from the study of patients with organic disease: yes vs. no; (iv) oral lactose load of 50 g vs. other load; (v) cohort study vs. (nested) case–control study design; (vi) QUADAS items 1, 2 or 5 (as described above).

Subgroup analyses were only performed when each subgroup included data of at least two diagnostic studies. In case each subgroup included data of at least four studies with homogenous results per

Table 1 Checklist for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (11) (modified version)

Item
1. Valid of selection and representativeness of study participants Score '+' if consecutive patients or a random sample have been selected and when the inclusion or exclusion criteria do not jeopardize the representativeness of the study participants.
2. Test review bias Score '+' if the index test results are interpreted blind to the results of the reference standard.
3. Incorporation bias Score '+' if the results of the index test were not part of the reference standard
4. Clinical review bias Score '+' if no additional clinical data are available, or if no usually available clinical data are missing.
5. The reference standard is likely to classify the target condition correctly Score '+' if the reference test is a lactose hydrogen breath test with (i) a lactose load of 50 g, (ii) a duration of at least 3 h and (iii) a cut-off score of >20 ppm above baseline level.
6. Partial verification bias Score '+' if it is clear that all patients or a random selection of those who received the index test went on to receive a reference standard.
7. Differential verification bias Score '+' if it is clear that all patients receiving the index test were subjected to the same reference standard.
8. Diagnostic review bias Score '+' if the reference standard results were interpreted blind to the results of the index test.
9. The time period between the index test and reference standard is short enough to be reasonably sure that the target condition did not change between the two tests Score '+' if the time period is 1 month or less.
10. Bias by withdrawals Score '+' if all patients who enrolled in the study received both the index test and the reference standard. In case of withdrawals: score the potential bias by these withdrawals.
11. Bias by missing values or uninterpretable test results Score '+' if all test results are reported for all patients who received the index test and reference standard (including uninterpretable results). In case of missings: score the potential bias by these missing values.

Each items is scored as '+' (no bias); '−' (potential bias); or '?'.

subgroup, we calculated per subgroup a pooled estimate of sensitivity and specificity using bivariate analyses. In case subgroups included data of less than four studies or data of at least four studies showing heterogeneous results on visual inspection, we presented per subgroup the range of sensitivity and specificity. Studies providing insufficient information on a factor were not included in that specific subgroup analysis.

Results

Literature search and study selection

The literature search yielded 695 references. A total of 114 full papers were retrieved of which 25 were considered relevant for the review.[8,17–40] Reference checking yielded two additional relevant papers.[41,42] With two papers reporting on the same study,[37,38] a total of 26 primary diagnostic studies were included in the review. A summary of the search results is presented in Figure 1.

To enable extraction of a two-by-two table, authors of 11 papers were asked for additional data.[21,25,26,32,41,43–48] Five of them were able and willing to grant our request.[21,25,26,32,41]

Study characteristics

Table 2 presents details of the primary diagnostic studies included in the review. None of the studies were performed in primary care, while two studies were population-based screening studies.[25,33] All but one[23] studies were cohort studies with prevalence of lactose malabsorption ranging from 4%[25] to 86%.[35] In 13 studies patients with organic diseases were explicitly excluded.[17,19,20,23–25,31,32,34,35,39,41,42]

The following index tests were studied: (i) symptoms as presented before the LHBT (11 studies); (ii) self-reported milk intolerance or degree of milk consumption (nine studies); and (iii) symptoms as reported during the LHBT and immediately thereafter (18 studies). In 5 of the 26 studies, LHBT was not the single reference standard to diagnose lactose malabsorption; these studies additionally used the results of methane excretion, a lactose tolerance

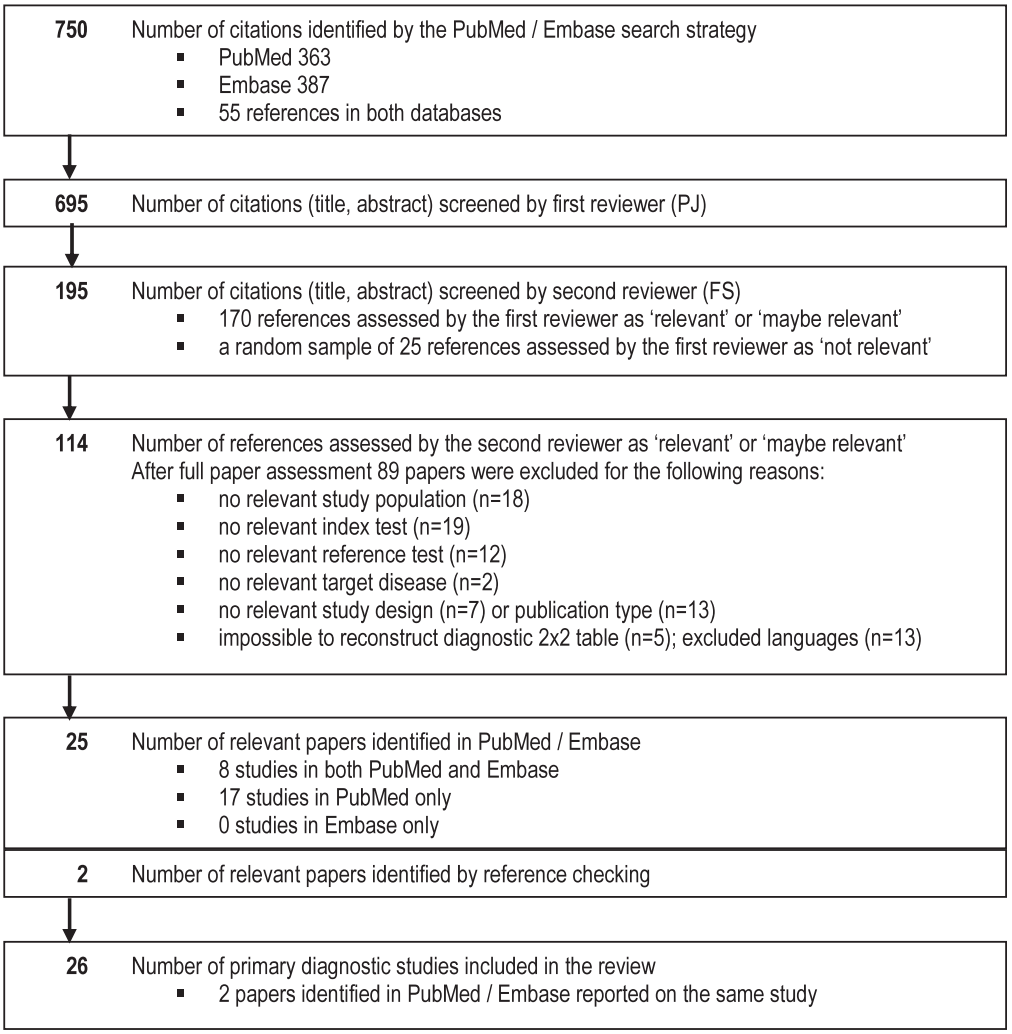

Figure 1. Flow diagram depicting search and selection processes.

test, biopsy, diet, X-ray.[19,23,25,27,33] An oral lactose load of 50 g was used in 18 studies,[18–22,24,26–37] while the dose was not reported in one study.[23]

Methodological quality of included studies

On average, the reviewers disagreed in 3 out of 11 items (range 1–6). Disagreements mainly concerned test review bias (item 2) and clinical review bias (item 4). All disagreements were resolved during consensus meetings. Table 3 presents the results of the quality assessment. Potential sources of bias most frequently related to the selection of study participants (item 1), clinical review bias (item 4), and the validity of the reference standard (item 5). The following aspects were poorly described (i.e. score 'unclear'): test review bias (item 2) and blind interpretation of reference test results (item 8). Generally, nine studies performed well receiving a positive assessment of at least 8 out of 11 QUADAS items.[18,22,27,30,32,34–37]

Pre-test GI symptoms

Table 4 presents the results of the 10 cohort studies and 1 case–control study that investigated the diagnostic performance of GI symptoms as presented before the LHBT test. Diarrhea, abdominal pain, bloating/distention, flatulence and constipation were investigated in at least four studies. Seven studies additionally reported on the diagnostic value of age, ethnicity or gender.

All four symptoms frequently associated with lactose intolerance showed very heterogeneous test results. For diarrhea[19,22–24,31,34,40] sensitivity ranged from 0.30 to 0.80 and specificity from 0.32 to 0.84; for abdominal pain[19,22,24,31,32] from 0.00 to 0.85 and from 0.18 to 0.73, respectively; for bloating[22–24,32,37] from 0.00 to 0.84 and from 0.18 to 0.96, respectively; for flatulence[22–24,32,37] from 0.10 to 0.90 and from 0.08 to 0.89, respectively. Due to this heterogeneity we refrained from statistical pooling.

Table 2 Characteristics of primary diagnostic studies included in the review

Author	Design	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Bernardes-Silva, 2007[17] Setting unclear Brazil, not reported when	Study design: cohort; sampling procedure: unclear; planning data-collection: prospective	Patients referred for hydrogen breath test. They were diagnosed with IBS by the Rome II criteria and after the exclusion of other organic disease	Organic disease. Patients should not have recently taken antibiotics/probiotics and should avoid gas-producing foods the day before the test	Enrolled: $n=75$; included in 2×2 table: $n=75$; mean age: 50 y (SD 14.2); sex: 59/75 women Prevalence LM: 41%	Index test(s): symptoms during LHBT Reference test(s): 25 g LHBT
Beyerlein, 2008[18] Gastrointestinal Function Unit, Switzerland, 1999–2005	Study design: cohort; sampling procedure: all patients; planning data-collection: prospective	Patients referred for hydrogen breath test. Patients were asked to be fasting, to refrain from smoking, use of antibiotics and laxatives	Patients with baseline LHBT samples ≥20 ppm	Enrolled: $n=1127$; included in 2×2 table: 1127; mean age: 40 (7–87); sex: 807/1127 women Prevalence LM: 33%	Index test(s): ethnicity, symptoms during LHBT Reference test(s): 50 g LHBT
Bianchi Porro, 1983[19] Hospitalized patients Italy, not reported when	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: unclear; planning data-collection: prospective	Hospitalized patients who had suffered from unspecific abdominal complaints for at least one year	Upper or lower organic GI disease; history of major abdominal surgery or high ethanol intake; diabetics	Enrolled: $n=77$; included in 2×2 table: $n=77$; mean age: 42 y (18–54); sex: 40/77 women Prevalence LM: 58%	Index test(s): predominant pre-test symptom, MI awareness Reference test(s): combination of 50 g LHBT, LTT, biopsy
Bozzani, 1986[20] Outpatient gastroenterology unit Italy, not reported when	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: consecutive; planning data-collection: prospective	Outpatients with IBS features: 12 month history at least of abdominal pain associated with distension, flatulence, borborygmi, altered bowel habit	Organic disease; GI surgery; relevant drug intake	Enrolled: $n=40$; included in 2×2 table: $n=40$; median age: 41 y (20-70); sex: 22/40 women Prevalence LM: 83%	Index test(s): milk intake Reference test(s): up to 50 g LHBT
Casellas, 2008[21] Digestive System Research Unit Spain, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Caucasian patients referred for LHBT. None had taken antibiotics or been prepared for radiologic or endoscopic examinations in last 2 weeks	None reported	Enrolled: $n\geq171$; included in 2×2 table: $n=171$; median age: 44; sex: 118/171 women Prevalence LM: 46%	Index test(s): symptoms during LHBT Reference test(s): 50 g LHBT
DiPalma, 1988[22] Subspecialty clinic USA, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Patients referred for undiagnosed abdominal complaints such as nonspecific abdominal pain or cramps, bloating, 'gas', altered bowel habits, flatulence	Patients referred for other GI problems (liver or pancreatic abnormalities, bleeding, polyps, malabsorption, cancer, GI procedures)	Enrolled: $n=242$; included in 2×2 table: $n=236$; mean age: 45 y (SD 15); sex: 173/242 women Prevalence LM: 66%	Index test(s): demographics, pre-test symptoms, MI awareness, symptoms during LHBT Reference test(s): 50 g LHBT

(continued)

Table 2 Continued

Author	Design	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Enck, 1988[23] Outpatient clinic USA, 1982–84	Study design: nested case-control; sampling procedure: unclear; planning data-collection: retrospective	Patients referred for irregular stool habits and abdominal pain. Only those with functional bowel disorder (FBD) or lactose malabsorption (LM) were included	Organic disease	Enrolled: $n=41$ (20 FBD, 21 LM); Included in 2×2 table: $n=37$; mean age: ?; sex: ? women Prevalence LM: n.a. (CC study)	Index test(s): pre-test symptoms, food intolerance awareness Reference test(s): combination of LHBT (dose unclear) and diet
Enck, 1990[24] Outpatient Gastroenterology clinic Germany, 1987–88	Study design: cohort; Sampling procedure: all; planning data-collection: prospective	All patients presenting with abdominal complaints of unknown origin—irregular stool habits and abdominal pain	Organic disease, specifically inflammations and tumors	Enrolled: $n=37$; included in 2×2 table: $n=37$; mean age: 39 y (15–69); $n=64$; sex: 35/64 women Prevalence LM: 24%	Index test(s): pre-test symptoms Reference test(s): 50 g LHBT
Farup, 2004[25] Population-based Screening Study Norway 2001	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: all; planning data-collection: prospective	Participants of a population-based health study fulfilling Rome II IBS criteria plus reporting alarm symptoms	Organic disease; origin out of Norway	Enrolled: $n=82$; included in 2×2 table: $n\geq72$; mean age: 49 y; sex: 56/82 women Prevalence LM: 4%	Index test(s): self-reported MI, symptoms during and after LHBT Reference test(s): 25 g LHBT, methane test
Fernández-Bañares, 2006[41] Outpatient gastroenterology Spain, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Patients who fulfill Rome II criteria for functional abdominal bloating. Blood analyses, serology of celiac disease, stool ova and parasites were negative	Abdominal pain or altered bowel habits; aerophagia; diabetes mellitus with autonomic dysfunction; digestive surgery; alcohol abuse; systemic diseases; bronchial asthma and use of inhaled therapies; organic bowel diseases; acute psychiatric illnesses	Enrolled: $n=36$; included in 2×2 table: $n=36$; mean age: 51 y (±3.1); sex: 24/36 women Prevalence LM: 39%	Index test(s): symptoms during LHBT Reference test(s): 20 g LHBT
Gupta, 2007[26] Setting unclear India, 2003–05	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: all; planning data-collection: prospective	Patients with IBS diagnosed using Rome II criteria	Basal H2 of >20 ppm	Enrolled: $n=127$; included in 2×2 table: $n\geq112$; mean age: 36 y (SD 11); sex: 34/124 women Prevalence: 72%	Index test(s): self-reported MI, symptoms during LHBT Reference test(s): 50 g LHBT
Hermans, 1997[27] GI laboratory Netherlands, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Adult patients with unexplained abdominal complaints who were referred consecutively from the GI outpatient clinic to the GI laboratory for assessment of lactose malabsorption	Subjects treated with antibiotic drugs; bowel preparation for an endoscopic or a radiological investigation within 4 weeks before the test; diabetes mellitus	Enrolled: $n=309$; included in 2×2 table: $n=309$; mean age: 42 y (SD 14); sex: 179/309 women Prevalence LM: 24%	Index test(s): symptoms during LHBT Reference test(s): combination of 50 g LHBT, LTT and X-ray

(continued)

Table 2 Continued

Author	Design	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Kerber, 2007[28] Outpatient department Austria, not reported when	Study design: cohort; sampling procedure: unclear; planning data-collection: prospective	Outpatients consulting for symptoms of IBS	Non-H2 producers	Enrolled: $n=135$; included in 2×2 table: $n=120$; mean age: 43 y (SD 16); sex: 94/120 women Prevalence LM: 50%	Index test(s): symptoms during and after LHBT Reference test(s): 50 g LHBT
Lerch, 1991[29] Gastroenterology service Germany, not reported when	Study design: cohort (originally four cohorts but we excluded three of them); sampling procedure: consecutive; planning data-collection:	Outpatients with vague, remitting abdominal symptoms of unknown origin	Outpatients with SIBO	Enrolled: $n\geq144$; included in 2×2 table: $n=144$; mean age 41 (16–76); sex: 73/144 women Prevalence LM: 36%	Index test(s): symptoms during and after LHBT Reference test: 50 g LHBT
Lisker, 1989[42] Gastroenterology outpatient clinic Mexico, not reported when	Study design: cohort?; sampling procedure: unclear; planning data-collection: prospective	(i) A diagnosis of IBS (chronic abdominal pain, altered bowel habits, no organic disease); (ii) diet had to include milk and/or dairy products; (iii) proper diet compliance during first month	Organic disease	Enrolled: $n=18$; included in 2×2 table: $n=12$; mean age: 49 y (24–72); sex: 9/12 female Prevalence LM: 67%	Index test(s): symptoms during LHBT Reference test(s): 12.5 g LHBT
Metz, 1975[30] Gastroenterology unit UK, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Patients investigated in the gastoenterology unit either for diarrhoea or abdominal symtoms of unknown cause	None reported	Enrolled: $n=25$; included in 2×2 table: $n=25$; mean age: ?; sex: ? women Prevalence LM: 40%	Index test(s): awareness of MI, symptoms during LHBT Reference test(s): 50 g LHBT
Newcomer, 1983[31] Division of Gastroenterology USA, 1979–80	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: unclear; planning data-collection: prospective	Each subject had had symptoms consistent with the irritabel bowel syndrome for at least 1 year and denied any history of MI	Organic disease; tenderness of the abdominal wall on physical examination	Enrolled: $n=80$; included in 2×2 table: $n=80$; mean age: 50 y (26–82); sex: 64/80 women Prevalence LM: 6%	Index test(s): predominant pre-test symptom Reference test(s): 50 g LHBT
Parker, 2001[32] Medical outpatients UK, not reported when	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	IBS patients (Rome criteria) referred for a LHBT	Organic GI disease	Enrolled: $n=122$; included in 2×2 table: $n=115$; age: 59/122 were 40 y or older; sex: 85/122 women Prevalence LM: 27%	Index test(s): pre-test symptoms Reference test(s): 50 g LHBT

(continued)

Table 2 Continued

Author	Design	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Pimentel, 2003[33] Population-based screening study USA, not reported when	Study design: cohort; sampling procedure: unclear; planning data-collection: prospective	Patients with diarrhea-predominant IBS (Rome II criteria) recruited through advertising in newsprint	History of risk factors for bacterial overgrowth	Enrolled: n = 25; included in 2x2 table: n = 19; mean age: 37 (SD 9); sex: 10/19 women Prevalence LM: 53% LM	Index test(s): symptoms during LHBT Reference test(s): 50 g LHBT or methane
Rana, 2001[34] Gastroenterology Hospital Clinic, India, 1989–90	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: consecutive; planning data-collection: prospective	Patients with IBS (history of abdominal pain, distension, alteration of bowel habits, mucus and normal baseline investigations)	Organic disease; history of MI; recent use of medications known to affect the GI function	Enrolled: $n = 25$; included in 2×2 table: $n = 25$; mean age: ?; sex: ? women Prevalence LM: 56%	Index test(s): diarrhea Reference test(s): 50 g LHBT
Sciarretta, 1984[35] Setting not reported; gastroenterology unit? Italy, not reported when	Study design: cohort (originally case-control, but we excluded healthy controls); sampling procedure: unclear; planning data-collection: prospective	Patients suffering from IBS (clinical picture and negative test results diagnostic work-up). High-fibre diets or other drugs were withdrawn during the test period	Organic disease	Enrolled: $n = 72$; included in 2×2 table: n = 72; mean age: 43 y (12–72); sex: 41/72 women Prevalence LM: 86%	Index test(s): MI awareness, symptoms during LHBT Reference test(s): up to 50 g LHBT
Szilagyi, 2005[36] SMBD Jewish General Hospital, Canada, 2002–04	Study design: cohort; sampling procedure: unclear; planning data-collection: prospective	Patients evaluated for LHBT	Patients with uncontrolled diabetes mellitus, uncontrolled thyroid disorders or pregnancy	Enrolled: $n = 125$; included in 2×2 table: $n = 118$; mean age: 42 y (18–85); sex: 75/118 women Prevalence LM: 50%	Index test(s): pre-test symptoms, symptoms during LHBT Reference test(s): 50 g LHBT
Tolliver 1994, 1996[37,38] Outpatient gastroenterology clinic at the College of Medicine, USA, 1989–92	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Patients were referred by family practitioners, general internists and gynaecologists for abdominal pain not previously evaluated. Patients had to meet IBS criteria: (i) abdominal pain relieved by defecation, or associated with change in frequency or consistency of stool; (ii) disturbed defecation involving two or more of the following: altered stool frequency, form or passage, passage of mucus	None reported	Enrolled: $n = 196$; included in 2×2 table: $n = 161$; mean age: 48 y; sex: 143/161 women Prevalence LM: 29%	Index test(s): pre-test symptoms Reference test(s): 50 g LHBT

(continued)

Table 2 Continued

Author	Design	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Vernia, 1995[39] Setting not reported Italy, 1987–91	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Patients suggestive of IBS (at least two of the following: abdominal distension and/or bloating; relief of pain with defecation; pain associated with more frquent or looser stools; alternating constipation and diarrhea; mucus in stools). No one was aware of LI and all used lactose-containing food	Alteration of blood analysis, positive FOBT, presence of ova or parasites, abnormal fibersigmoidoscopy and/or DCBE	Enrolled: $n=230$; included in 2×2 table: $n=230$ (incl. 22 non-producers); mean age: 38 y (SD 8.6); sex: 159/230 women Prevalence LM: 68%	Index test(s): symptoms during and after LHBT Reference test(s): up to 25 g LHBT
Vernia, 2001[40] Specialty gastoenterology clinic Italy, 1990–98	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Outpatients referred to specialty GI clinic who fulfilled IBS (i.e. Rome) criteria and who regularly consumed milk (or lactose-containing milk derivatives) (NB: we excluded studygroup consisting solely of patients with self-reported MI)	Patients with a combination of IBS (Rome criteria) and self-reported MI	Enrolled: $n=503$; included in 2×2 table: $n=503$ (incl. 23 non-producers); mean age: 36 y (SD 14); sex: 336/503 women Prevalence LM: 67%	Index test(s): Predominant pre-test symptom, symptoms during and after LHBT Reference test(s): up to 25 g LHBT
Vernia, 2004[38] Tertiary referral centre Italy, 1996–2001	Study design: cohort; sampling procedure: consecutive; planning data-collection: prospective	Consecutive outpatients with a diagnosis of IBS (Rome criteria). Data analysed in age- and sex-matched pairs, classified according to MI awareness	None reported	Enrolled: $n=475$; included in 2×2 table: $n=402$ (incl. eight non-producers); mean age: 35 y; sex: 282/402 women Prevalence LM: 61%	Index test(s): MI awareness, symptoms during and after LHBT Reference test(s): up to 25 g LHBT

LM: lactose malabsorption; GI: gastrointestinal; MI: milk intolerance; IBS: irritable bowel syndrome; LTT: lactose tolerance test; LHBT: lactose hydrogen breath test; SD: standard deviation; y: years; n.a.: not applicable; CC study: case–control; sub: subgroup.

Table 3 Results of the quality assessment per study[a]

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11
Bernardes-Silva, 2007[17]	?	?	+	−	−	+	+	?	+	+	+
Beyerlein, 2008[b,18]	+	?	+	+	+	+	+	?	+	+	+
Bianchi Porro, 1983[19]	−	+	+	−	−	+	−	?	?	+	+
Bozzani, 1986[20]	−	+	+	−	+	+	−	?	?	+	+
Casellas, 2008[21]	?	?	+	+	−	+	+	?	+	+	?
DiPalma, 1988[b,22]	+	+	+	+	+	+	+	?	?	+	+
Enck, 1988[23]	?	?	+	?	−	+	−	?	?	?	?
Enck, 1990[24]	?	?	+	?	+	+	+	?	?	+	+
Farup, 2004[25]	−	+	+	−	−	+	−	?	+	+	+
Fernández-Bañares, 2006[41]	−	?	+	?	−	+	+	?	+	+	+
Gupta, 2007[26]	?	?	+	?	+	+	+	?	+	+	+
Hermans, 1997[b,27]	+	?	+	+	−	+	+	?	+	+	+
Kerber, 2007[28]	?	?	+	?	+	+	+	?	+	+	−
Lerch, 1991[29]	?	?	+	?	+	+	+	?	+	+	+
Lisker, 1989[42]	−	+	+	−	−	+	+	?	+	−	+
Metz, 1975[b,30]	+	+	+	+	+	+	+	?	+	+	+
Newcomer, 1983[31]	−	+	+	−	+	+	+	?	?	+	+
Parker, 2001[b,32]	+	+	+	+	+	+	+	?	+	+	+
Pimentel, 2003[33]	?	?	+	?	−	+	−	?	+	−	+
Rana, 2001[b,34]	−	+	+	+	+	+	+	+	?	+	+
Sciarretta, 1984[b,35]	−	+	+	−	+	+	+	?	+	+	+
Szilagyi, 2005[36]	?	?	+	+	+	+	+	?	+	+	+
Tolliver, 1994,1996[b,37,38]	+	+	+	+	+	+	+	?	?	+	−
Vernia, 1995[39]	−	?	+	−	−	+	+	?	+	+	+
Vernia, 2001[40]	?	+	+	+	−	+	+	?	?	+	+
Vernia, 2004[8]	+	?	+	+	−	+	+	?	?	+	+

'+': no bias; '−': potential bias; '?': bias unclear.
[a]See Table 1 for explanation of quality items.
[b]Study received a positive assessment on ≥8 of the 11 quality items.

In the category 'other GI symptoms' (Table 4) constipation[23,24,31,40] or alternating diarrhea and constipation,[24,40] considered indicative of IBS, appeared to be often absent in those with lactose malabsorption (range sensitivity 0.00–0.22), but also in those without lactose malabsorption (range specificity 0.75–0.94). Statistical pooling of the four studies on constipation resulted in a sensitivity of 0.13 (95% CI 0.07–0.23) and a specificity of 0.83 (95% CI 0.75–0.89). Of the sociodemographic variables specificity of ethnicity was high ranging from 0.77 to 0.96, indicating that a non-Caucasian ethnic origin may be associated with the presence of lactose malabsorption.[18,22,24,37]

Self-reported milk intolerance

Table 4 presents the results of the studies that investigated the diagnostic performance of self-reported milk intolerance (seven studies) or degree of milk consumption (three studies). Eight studies were cohort studies;[8,19,20,22,25,26,30,35] one a case–control study.[23]

As results for sensitivity ranged from 0.30 to 0.71, and for specificity from 0.25 to 0.87, we had to refrain from statistical pooling. The risk for lactose malabsorption among those with self-reported milk intolerance or reporting no or less milk consumption ranged from 0.62 to 0.92, while the risk among those reporting to be milk tolerant or had (normal) milk consumption varied from 0.32 to 0.79. The values reported by Farup *et al.*[25] are, however, much lower (0.06 and 0.03, respectively). In this screening-based study, the prevalence of lactose malabsorption (4%) was substantially lower than in the other studies (40–86%).

Lactose intolerance vs. malabsorption

Table 4 presents the results of 18 studies that investigated the relationship between symptoms after lactose ingestion and the results of the LHBT. All were cohort studies; none were performed in a primary care setting.

About 33–97% of the patients with a positive LHBT result reported symptoms after lactose

Table 4 Diagnostic performance of GI symptoms, age, ethnicity, gender, milk intolerance awareness and the presence of symptoms during the hydrogen breath test

Index test	Author	TP	FP	FN	TN	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	1-NPV (95% CI)
GI symptoms characteristic for LM (presence vs. absence)									
Diarrhoea	DiPalma, 1988[22]	98	52	57	29	0.63 (0.55–0.71)	0.36 (0.25–0.47)	0.65 (0.57–0.73)	0.66 (0.55–0.76)
Diarrhoea	Enck, 1988[23]	6	4	13	14	0.32 (0.13–0.57)	0.78 (0.52–0.94)	n.a.	n.a.
Diarrhoea	Enck, 1990[24]	5	19	4	9	0.56 (0.21–0.86)	0.32 (0.16–0.52)	0.21 (0.07–0.42)	0.31 (0.09–0.61)
Diarrhoea	Rana, 2001[34]	9	2	5	9	0.64 (0.35–0.87)	0.82 (0.48–0.98)	0.82 (0.48–0.98)	0.36 (0.13–0.65)
Intermittent diarrhoea	Bianchi Porro, 1983[19]	19	5	26	27	0.42 (0.28–0.58)	0.84 (0.67–0.95)	0.79 (0.58–0.93)	0.49 (0.35–0.63)
– All lower functional disorder: diarrhoea	Bianchi Porro, 1983[a,19]	19	5	15	7	0.56 (0.38–0.73)	0.58 (0.28–0.85)	0.79 (0.58–0.93)	0.68 (0.45–0.86)
Predominant symptom: diarrhoea	Newcomer, 1983[31]	4	15	1	60	0.80 (0.28–0.99)	0.80 (0.69–0.88)	0.21 (0.06–0.46)	0.02 (0.00–0.09)
Predominant symptom: diarrhoea	Vernia, 2001[40]	79	46	258	120	0.23 (0.19–0.28)	0.72 (0.65–0.79)	0.63 (0.54–0.72)	0.68 (0.63–0.73)
Abdominal pain	Enck, 1990[24]	6	17	3	11	0.67 (0.30–0.93)	0.39 (0.22–0.59)	0.26 (0.10–0.48)	0.21 (0.05–0.51)
Abdominal pain	Parker, 2001[32]	22	69	9	15	0.71 (0.52–0.86)	0.18 (0.10–0.28)	0.24 (0.16–0.34)	0.38 (0.19–0.59)
Predominant symptom: abdominal pain	Newcomer, 1983[31]	0	20	5	55	0.00 (0.00–0.52)	0.73 (0.62–0.83)	0.00 (0.00–0.17)	0.08 (0.03–0.18)
Colicky abdominal pain	Bianchi Porro, 1983[19]	21	9	24	23	0.47 (0.32–0.62)	0.72 (0.53–0.86)	0.70 (0.51–0.85)	0.51 (0.36–0.66)
– All lower functional disorder: colicky pain	Bianchi Porro, 1983[a,19]	21	9	13	3	0.62 (0.45–0.78)	0.25 (0.06–0.57)	0.70 (0.51–0.85)	0.81 (0.54–0.96)
Cramps	DiPalma, 1988[22]	131	60	24	21	0.85 (0.78–0.90)	0.26 (0.17–0.37)	0.69 (0.62–0.75)	0.53 (0.38–0.68)
Bloating	DiPalma, 1988[22]	121	60	34	21	0.78 (0.71–0.84)	0.26 (0.17–0.37)	0.67 (0.60–0.74)	0.62 (0.48–0.75)
Bloating	Enck, 1990[24]	6	12	3	16	0.67 (0.30–0.93)	0.57 (0.37–0.76)	0.33 (0.13–0.59)	0.16 (0.03–0.40)
Bloating	Tolliver, 1994[37]	0	5	47	109	0.00 (0.00–0.08)	0.96 (0.90–0.99)	0.00 (0.00–0.52)	0.30 (0.23–0.38)
Distension	Enck, 1988[23]	14	14	5	4	0.74 (0.49–0.91)	0.22 (0.06–0.48)	n.a.	n.a.
Distension	Parker, 2001[32]	26	69	5	15	0.84 (0.66–0.95)	0.18 (0.10–0.28)	0.27 (0.19–0.38)	0.25 (0.09–0.49)
Flatulence	DiPalma, 1988[22]	15	9	140	72	0.10 (0.06–0.16)	0.89 (0.80–0.95)	0.63 (0.41–0.81)	0.66 (0.59–0.72)
Flatulence	Enck, 1988[23]	13	13	6	5	0.68 (0.43–0.87)	0.28 (0.10–0.54)	n.a.	n.a.
Flatulence	Enck, 1990[24]	5	8	4	20	0.56 (0.21–0.86)	0.71 (0.51–0.87)	0.39 (0.14–0.68)	0.17 (0.05–0.37)
Flatulence	Parker, 2001[32]	28	77	3	7	0.90 (0.74–0.98)	0.08 (0.03–0.16)	0.27 (0.19–0.36)	0.30 (0.07–0.65)
Flatulence	Tolliver, 1994[37]	18	40	29	74	0.38 (0.25–0.54)	0.65 (0.56–0.74)	0.31 (0.20–0.45)	0.28 (0.20–0.38)
Gas	DiPalma, 1988[a,22]	131	69	24	12	0.85 (0.78–0.90)	0.15 (0.08–0.24)	0.66 (0.59–0.72)	0.67 (0.49–0.81)
Predominant symptom: gas/bloating	Newcomer, 1983[31]	1	26	4	49	0.20 (0.01–0.72)	0.65 (0.54–0.76)	0.04 (0.00–0.19)	0.08 (0.02–0.18)
Predominant symptom: pain/gas/bloating	Vernia, 2001[40]	150	75	187	91	0.45 (0.39–0.50)	0.55 (0.47–0.63)	0.67 (0.60–0.73)	0.67 (0.61–0.73)
Other GI symptoms (presence vs. absence)									
Constipation	Enck, 1988[23]	4	4	15	14	0.21 (0.06–0.46)	0.78 (0.52–0.94)	n.a.	n.a.
Constipation	Enck, 1990[24]	2	7	7	21	0.22 (0.03–0.60)	0.75 (0.55–0.89)	0.22 (0.03–0.60)	0.25 (0.11–0.45)
Predominant symptom: constipation	Newcomer, 1983[31]	0	14	5	61	0.00 (0.00–0.52)	0.81 (0.71–0.89)	0.00 (0.00–0.23)	0.08 (0.03–0.17)
Predominant symptom: constipation	Vernia, 2001[40]	45	22	292	144	0.13 (0.10–0.18)	0.87 (0.81–0.92)	0.67 (0.55–0.78)	0.67 (0.62–0.71)
Alternating diarrhoea/constipation	Enck, 1990[24]	1	5	8	23	0.11 (0.00–0.48)	0.82 (0.63–0.94)	0.17 (0.00–0.64)	0.26 (0.12–0.45)
Predominant symptom: alternating diarrhoea/constipation	Vernia, 2001[40]	63	23	274	143	0.19 (0.15–0.23)	0.86 (0.80–0.91)	0.73 (0.63–0.82)	0.66 (0.61–0.70)
Feeling of incomplete evacuation	Enck, 1988[23]	11	9	8	9	0.58 (0.34–0.80)	0.50 (0.26–0.74)	n.a.	n.a.
Incomplete defecation	Tolliver, 1994[37]	14	30	33	84	0.30 (0.17–0.45)	0.74 (0.65–0.82)	0.32 (0.19–0.48)	0.28 (0.20–0.37)
Mucus	Enck, 1988[23]	7	7	12	11	0.37 (0.16–0.62)	0.61 (0.36–0.83)	n.a.	n.a.
Mucus	Tolliver, 1994[37]	23	42	24	72	0.49 (0.34–0.64)	0.63 (0.54–0.72)	0.35 (0.24–0.48)	0.25 (0.17–0.35)

(continued)

Table 4 Continued

Index test	Author	TP	FP	FN	TN	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	1-NPV (95% CI)
Pain relief by defecation	Enck, 1988[23]	12	7	7	11	0.63 (0.38–0.84)	0.61 (0.36–0.83)	n.a.	n.a.
Pain relief by defecation	Tolliver, 1994[37]	11	22	36	92	0.23 (0.12–0.38)	0.81 (0.72–0.88)	0.33 (0.18–0.52)	0.28 (0.21–0.37)
Pain associated with looser stools	Enck, 1988[23]	4	6	15	12	0.21 (0.06–0.46)	0.67 (0.41–0.87)	n.a.	n.a.
Pain associated with more stools	Enck, 1988[23]	5	6	14	12	0.26 (0.09–0.51)	0.67 (0.41–0.87)	n.a.	n.a.
Altered bowel habit	Tolliver 1994[37]	2	1	45	113	0.04 (0.01–0.15)	0.99 (0.95-1.00)	0.67 (0.09–0.99)	0.29 (0.22–0.36)
Urgency	Parker, 2001[32]	24	62	7	22	0.77 (0.59–0.90)	0.26 (0.17–0.37)	0.28 (0.19–0.39)	0.24 (0.10–0.44)
Meteorism	Enck, 1988[23]	6	3	13	15	0.32 (0.13–0.57)	0.83 (0.59–0.96)	n.a.	n.a.
Dyspepsia	Bianchi Porro, 1983[19]	11	20	34	12	0.24 (0.13–0.40)	0.38 (0.21–0.56)	0.36 (0.19–0.55)	0.74 (0.59–0.86)
Sociodemographic variables									
Aged ≥40 vs. <40	Parker, 2001[32]	16	43	17	46	0.49 (0.31–0.67)	0.52 (0.41–0.62)	0.27 (0.16–0.40)	0.27 (0.17–0.40)
Ethnicity: non-Swiss vs. Swiss	Beyerlein, 2008[18]	207	174	169	577	0.55 (0.50–0.60)	0.77 (0.74–0.80)	0.54 (0.49–0.59)	0.23 (0.20–0.26)
Ethnicity: moderate/high risk vs. low risk	DiPalma, 1988[22]	50	8	97	60	0.34 (0.26–0.42)	0.88 (0.78–0.95)	0.86 (0.75–0.94)	0.62 (0.54–0.69)
Ethnicity: non-German vs. German	Enck, 1990[24]	3	1	6	27	0.33 (0.08–0.70)	0.96 (0.82-1.00)	0.75 (0.19–0.99)	0.18 (0.07–0.36)
Ethnicity: caucasian no vs. yes	Tolliver, 1994[37]	18	12	29	102	0.38 (0.25–0.54)	0.90 (0.82–0.94)	0.60 (0.41–0.77)	0.22 (0.15–0.30)
Gender: female vs. male	DiPalma, 1988[22]	114	59	47	22	0.71 (0.63–0.78)	0.27 (0.18–0.38)	0.66 (0.58–0.73)	0.68 (0.56–0.79)
Gender: female vs. male	Parker, 2001[32]	25	60	8	29	0.76 (0.58–0.89)	0.33 (0.23–0.43)	0.29 (0.20–0.40)	0.22 (0.10–0.38)
Gender: female vs. male	Szilagyi, 2005[36]	37	36	22	23	0.63 (0.49–0.75)	0.39 (0.27–0.53)	0.51 (0.39–0.63)	0.49 (0.34–0.64)
Gender: female vs. male	Vernia, 1995[39]	110	52	47	21	0.70 (0.62–0.77)	0.29 (0.19–0.41)	0.68 (0.60–0.75)	0.69 (0.57–0.80)
Milk intolerance awareness (yes vs. no)									
MI awareness	Bianchi Porro, 1983[19]	32	7	13	25	0.71 (0.56–0.84)	0.78 (0.60–0.91)	0.82 (0.67–0.93)	0.34 (0.20–0.51)
Awareness of lactose-associated symptoms	DiPalma, 1988[22]	48	29	113	52	0.30 (0.23–0.38)	0.64 (0.53–0.75)	0.62 (0.51–0.73)	0.69 (0.61–0.76)
Awareness of food intolerance	Enck, 1988[23]	8	6	11	12	0.42 (0.20–0.67)	0.67 (0.41–0.87)	n.a.	n.a.
Self-reported MI	Farup, 2004[25]	2	30	1	39	0.67 (0.09–0.99)	0.57 (0.44–0.68)	0.06 (0.01–0.21)	0.03 (0.00–0.13)
Self-reported MI	Gupta, 2007[26]	39	17	43	13	0.48 (0.36–0.59)	0.43 (0.26–0.63)	0.70 (0.56–0.81)	0.77 (0.64–0.87)
Self-reported MI	Metz, 1975[30]	4	2	6	13	0.40 (0.12–0.74)	0.87 (0.60–0.98)	0.67 (0.22–0.96)	0.32 (0.13–0.57)
Self-reported MI	Vernia, 2004[8]	152	49	138	63	0.52 (0.47–0.58)	0.56 (0.47–0.66)	0.76 (0.69–0.81)	0.69 (0.62–0.75)
Daily milk intake <250 vs. >250 ml	Bozzani, 1986[20]	24	2	11	3	0.69 (0.51–0.83)	0.60 (0.15–0.95)	0.92 (0.75–0.99)	0.79 (0.49–0.95)
Milk consumption: no vs. yes	Sciarretta, 1984[35]	40	4	22	6	0.65 (0.51–0.76)	0.60 (0.26–0.88)	0.91 (0.78–0.98)	0.79 (0.59–0.92)
Milk consumption: no vs. yes	Bianchi Porro, 1983[a,19]	32	24	13	8	0.71 (0.56–0.84)	0.25 (0.12–0.43)	0.57 (0.43–0.70)	0.62 (0.38–0.82)
Symptoms during and after LHBT (yes vs. no)									
Symptoms during LHBT	Bernardes-Silva, 2007[17]	28	8	3	36	0.90 (0.74–0.98)	0.82 (0.67–0.92)	0.78 (0.61–0.90)	0.08 (0.02–0.21)
Symptoms during LHBT	Beyerlein, 2008[18]	338	463	38	288	0.90 (0.86–0.93)	0.38 (0.35–0.42)	0.42 (0.39–0.46)	0.12 (0.08–0.16)
Symptoms during LHBT	Casellas, 2008[21]	76	66	2	27	0.97 (0.91–0.99)	0.29 (0.20–0.39)	0.54 (0.45–0.62)	0.07 (0.01–0.23)
– Symptom score during LHBT ≥7	Casellas, 2008[a,21]	60	30	18	63	0.77 (0.66–0.86)	0.68 (0.57–0.77)	0.67 (0.56–0.76)	0.22 (0.14–0.33)
Symptoms during LHBT	DiPalma, 1988[22]	124	13	31	68	0.80 (0.73–0.86	0.84 (0.74–0.91)	0.91 (0.84–0.95)	0.31 (0.22–0.41)
Symptoms during LHBT and 24 h thereafter	Farup, 2004[25]	2	26	1	44	0.67 (0.09–0.99)	0.63 (0.51–0.74)	0.07 (0.01–0.24)	0.02 (0.00–0.12)
Symptoms during LHBT	Fernandez, 2006[41]	7	3	7	19	0.50 (0.23–0.77)	0.86 (0.65–0.97)	0.70 (0.35–0.93)	0.27 (0.12–0.48)
Symptoms during LHBT	Gupta, 2007[26]	48	20	41	15	0.54 (0.43–0.65)	0.43 (0.26–0.61)	0.71 (0.58–0.81)	0.73 (0.60–0.84)
Symptoms during LHBT	Hermans, 1997[27]	67	162	8	72	0.89 (0.80–0.95)	0.31 (0.25–0.37)	0.29 (0.24–0.36)	0.10 (0.04–0.19)

(continued)

Table 4 Continued

Index test	Author	TP	FP	FN	TN	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	1-NPV (95% CI)
Symptoms during LHBT and 12 h thereafter	Kerber, 2007[28]	54	9	6	51	0.90 (0.80–0.96)	0.85 (0.73–0.93)	0.86 (0.75–0.93)	0.11 (0.04–0.22)
Symptoms during LHBT and 3 h thereafter	Lerch,1991[29]	41	14	11	78	0.79 (0.65–0.89)	0.85 (0.76–0.91)	0.75 (0.61–0.85)	0.12 (0.06–0.21)
Symptoms during LHBT	Lisker, 1989[42]	4	0	4	4	0.50 (0.16–0.84)	1.00 (0.40–1.00)	1.00 (0.40–1.00)	0.50 (0.16–0.84)
Symptoms during LHBT	Metz, 1975[30]	8	1	2	14	0.80 (0.44–0.98)	0.93 (0.68–1.00)	0.89 (0.52–1.00)	0.13 (0.02–0.38)
Symptoms during LHBT	Pimentel, 2003[33]	8	3	2	6	0.80 (0.44–0.98)	0.67 (0.30–0.93)	0.73 (0.39–0.94)	0.25 (0.03–0.65)
Symptoms during LHBT and 1 h thereafter	Sciarretta, 1984[25]	25	0	37	10	0.40 (0.28–0.54)	1.00 (0.69–1.00)	1.00 (0.86–1.00)	0.79 (0.64–0.89)
Symptoms during LHBT	Szilagyi, 2005[36]	53	35	6	24	0.90 (0.80–0.96)	0.41 (0.28–0.54)	0.60 (0.49–0.71)	0.20 (0.08–0.39)
Symptoms during LHBT and 4 h thereafter	Vernia, 1995[39]	52	8	105	65	0.33 (0.26–0.41)	0.89 (0.80–0.95)	0.87 (0.75–0.94)	0.62 (0.54–0.69)
Symptoms during LHBT and 4 h thereafter	Vernia, 2001[40]	193	34	144	132	0.57 (0.52–0.63)	0.80 (0.73–0.85)	0.85 (0.80–0.89)	0.52 (0.46–0.58)
Symptoms during LHBT and 4 h thereafter	Vernia, 2004[28]	121	46	169	66	0.42 (0.36–0.48)	0.59 (0.49–0.68)	0.73 (0.65–0.79)	0.72 (0.66–0.78)

TP: true positive; FP: false positive; FN: false negative; TN: true negative; Se: sensitivity (i.e. proportion of those with lactose malabsorption who have a positive test result on index test); Sp: specificity (i.e. proportion of those without lactose malabsorption who have a negative test result on index test); PPV: positive predictive value (i.e. probability of lactose malabsorption in those with a positive test result on index test); 1-NPV: 1-negative predictive value (i.e. probability of lactose malabsorption in those with a negative test result on index test); CI: confidence interval; GI: gastrointestinal; LM: lactose malabsorption; sub: subgroup; MI: milk intolerance; IBS: irritable bowel syndrome; n.a.: not applicable due to case–control study design; LHBT: lactose hydrogen breath test.
[a]Not eligible for subgroup analyses (as the study would otherwise be included in the analysis more than once).

ingestion (sensitivity). We defined these as lactose intolerants. On the other hand, 0–71% of the lactose absorbers also appeared to report symptoms (1-specificity). Except for three studies[18,25,27], the presence of symptoms after lactose ingestion was more strongly associated with a positive than a negative LHBT result [range positive predictive value (PPV) 0.54–1.0]. For the three studies in which this was not the case (i.e. PPV < 0.50), the presence of lactose malabsorption among those with symptoms after lactose ingestion was still about three times more likely than among those without symptoms after lactose ingestion [PPV/(1 − NPV)].

Pre-planned subgroup analyses

Due to lack of data in one or both response categories many pre-planned clinical and methodological subgroup analyses could not be performed. In Table 5, the results are presented for the subgroup analyses for which sufficient data were available. For none of the subgroup analyses the results for both sensitivity and specificity were sufficiently homogeneous to calculate pooled estimates. The factor 'validity of the study sample' (QUADAS item 1), however, seemed to explain some of the variation in diagnostic performance across studies: two studies[22,32] with a valid study sample reported higher values for sensitivity but lower values for specificity of abdominal pain compared to the other two studies.[19,31]

Discussion

The diagnostic performance of symptoms reported to be associated with lactose intolerance (diarrhea, abdominal pain, bloating and flatulence) was highly variable. More firm associations were found for ethnicity: lactose malabsorption is more likely when a patient is of non-Caucasian ethnic origin. Self-reported milk intolerance and occurrence of symptoms during LHBT were not only found in lactose malabsorbers but also in lactose absorbers. Overall, however, their presence is more often associated with lactose malabsorption than absorption.

Diagnostic performance of tests in primary care

Our systematic review cannot provide evidence that is directly relevant for primary care physicians, as none of the studies were performed in primary care populations. This is remarkable as in many countries patients will first present their lactose related symptoms to a primary care physician, with

Table 5 Pre-planned subgroup analyses for which sufficient data were available

Subgroup analyses		Sensitivity (range)		Specificity (range)	
Prevalence	*No. of studies*	*<30%*	*>30%*	*<30%*	*>30%*
Diarrhoea	6 (2 vs. 4)	0.56–0.80	0.30–0.64	0.32–0.80	0.36–0.84
Abdominal pain	5 (3 vs. 2)	0.00–0.71	0.47–0.85	0.18–0.73	0.26–0.72
Symptoms after lactose ingestion	18 (2 vs. 16)	0.67–0.89	0.33–0.97	0.31–0.63	0.29–1.00
Exclusion of organic disease		*Explicit exclusion*	*No explicit exclusion*	*Explicit exclusion*	*No explicit exclusion*
Self-reported milk intolerance	8 (5 vs. 3)	0.42–0.71	0.40–0.52	0.57–0.78	0.43–0.87
Symptoms after lactose ingestion	17 (6 vs. 11)	0.33–0.90	0.42–0.97	0.63–1.00	0.31–0.93
Lactose load		*50 g*	*<50 g*	*50 g*	*<50 g*
Self-reported milk intolerance	8 (6 vs. 2)	0.30–0.71	0.52–0.67	0.43–0.87	0.56–0.57
Symptoms after lactose ingestion	18 (11 vs. 7)	0.40–0.97	0.33–0.90	0.31–1.00	0.59–1.00
Validity of sample (QUADAS 1)		*Score +*	*Score −*	*Score +*	*Score −*
Abdominal pain	4 (2 vs. 2)	0.71–0.85	0.00–0.47	0.18–0.26	0.72–0.73
Self-reported milk intolerance	7 (3 vs. 4)	0.30–0.52	0.65–0.71	0.56–0.87	0.60–0.78
Symptoms after lactose ingestion	10 (5 vs. 5)	0.42–0.90	0.33–0.67	0.31–0.93	0.63–1.00
Validity of reference test (QUADAS 5)		*Score +*	*Score −*	*Score +*	*Score −*
Diarrhoea	7 (4 vs. 3)	0.56–0.80	0.30–0.42	0.32–0.82	0.70–0.84
Constipation	4 (2 vs. 2)	0.00–0.21	0.10–0.21	0.75–0.81	0.78–0.89
Self-reported milk intolerance	9 (5 vs. 4)	0.30–0.69	0.42–0.71	0.43–0.87	0.56–0.78
Symptoms after lactose ingestion	17 (8 vs. 9)	0.40–0.90	0.33–0.97	0.38–1.00	0.29–1.00

sub: subgroup; score '+': no potential bias; score '−': potential bias.

most of them being subsequently managed in primary care. In general, performance of diagnostic tests in secondary care is not easily transferable to primary care. Especially the predictive values of a test are strongly dependent on the prevalence of disease. In a setting with a low disease prevalence the same combination of sensitivity and specificity will lead to much lower positive predictive values compared with a setting with a high disease prevalence. Prevalence rates in the retrieved studies were remarkably high; 13 of the 26 studies reported prevalence rates of 50% or higher while only two studies reported a rate of <20%.[25,31] Explanation for these high rates may be the studies' care setting, their strict in- and exclusion criteria, and the countries in which the studies were performed (see Discussion section).

Potential sources of bias

A first potential source of bias is the patient population included in the individual studies. In many studies (extensive) diagnostic work-up was used to exclude all possible organic diseases, which left a study sample consisting of patients with functional bowel disorders. As the presenting symptoms of patients with functional bowel disorders will be more homogeneous than the symptoms of all patients consulting for non-acute abdominal symptoms, the diagnostic performance of the presenting symptoms may be negatively influenced. Furthermore, by excluding all patients with organic disease the study design is actually changed from a cohort design into a nested case–control design, with accompanying consequences for prevalence rates. To investigate the potential bias of explicit exclusion of patients with organic disease we performed a subgroup analysis. Unfortunately, the results within the response categories were still too heterogeneous to pool the results. Finally, the so-called referral filter may have biased the diagnostic performance of self-reported milk intolerance; study populations of individual studies may have solely been composed of patients for whom this relationship was unclear as patients for whom there was not diagnostic uncertainty may not have been referred.

A second potential source of bias concerns the way tests were performed in the individual studies. Vernia *et al.*[8] mentioned that symptoms were trivial in most instances and that the occurrence of symptoms was likely to be overestimated as patients were encouraged to report 'any' symptom. This may have influenced the diagnostic performance of GI symptoms and the relationship between lactose malabsorption and intolerance. The use of a 50-g test dose has been criticized, especially for studies investigating symptoms, because it is equivalent to four to five servings (1 l of milk) which is far more

than an individual usually ingests at one time.[49] We studied the influence of lactose load on the relationship between self-reported milk intolerance and lactose malabsorption, as well as between symptoms during the LHBT and lactose malabsorption. Although the results within the response categories were still too heterogeneous to pool, we believe that an 'overload' of 50 g is necessary to obtain reliable test results for detecting lactose malabsorption. In lactose malabsorbers this load guarantees that intestinal processes will not be able to compensate for the low lactase levels, while this load should not bother lactose absorbers. In those diagnosed with lactose intolerance (i.e. those with a positive LHBT result and reporting symptoms during the test), an important next step is the determination of each individual's threshold lactose dose in order to introduce that dose in the diet.[35] However, a 50 g lactose load could lead to relatively high numbers of 'false-positive' tests necessitating further diagnostic testing in a large number of subjects. The recommended dosage of 25 g[10] is therefore an acceptable compromise. One may also comment on the LHBT itself, which is currently considered to be the diagnostic method of choice. However, as lactose intolerance is of greater clinical interest than lactose malabsorption, one may argue that it would clinically be more relevant to use 'report of symptoms during a positive LHBT result', or 'disappearing of symptoms by a long-term lactose restricted diet after a positive LHBT' as reference standard in diagnostic accuracy studies.

The final potential source of bias we like to discuss is the country in which the study was performed. As mentioned before, prevalence rates of lactose malabsorption are strongly related to ethnicity. Indeed, in our review we found high specificity values for non-Caucasian populations. Additionally, higher prevalence rates were found in studies performed in Mediterranean countries ($n = 8$, range 39–86%) compared to those performed in Northwestern Europe ($n = 6$, range 4–40%). Considering these differences one should be very cautious to generalize findings across countries. Additionally, one would expect different clinical routine across countries, with lactose breath testing more generally implemented in Mediterranean countries than in Northwestern Europe.

Strength and weaknesses review

In this review, where possible we adhered to the most recent guidelines for conducting a diagnostic review as described in the Cochrane Diagnostic Reviewers' Handbook. We used an extensive search strategy, but included a methodological filter to increase its specificity. By reference checking we tried to track down those publications our search strategy had failed to identify. We took into account the generally poor reporting of diagnostic accuracy studies[50] by excluding quality assessment scores 'unclear' from methodological subgroup analyses for the QUADAS tool.

The inclusion criteria of our review reflect our priority for gathering diagnostic performance data that are relevant to clinical practice. We solely extracted or reconstructed diagnostic data collected from symptomatic patients, excluding information from healthy controls. This decision resulted in less favorable results for specificity than sometimes presented in the original publications, or even led to exclusion of studies. Our inclusion criteria were strict in order to increase clinical relevance of the review, but the criteria also permitted us to include studies that were conducted with another research objective but fulfilling our criteria and providing enough data for a relevant diagnostic two-by-two table. We also used strict criteria to define our target disease. We defined lactose malabsorption as a positive LHBT result, thereby excluding literature on lactose malabsorption as defined by a positive blood glucose tolerance test. Whereas lactose intolerance appears to be imprecisely defined in medical literature—in several reviews lactose malabsorption and intolerance were used as synonyms—we decided to define lactose intolerance as a combination of a positive LHBT result (i.e. lactose malabsorption) plus accompanying clinical symptoms. Although this definition may not be generally applied, we believe that use of explicit and clinically meaningful definitions are inevitable if one wants to gather evidence on its diagnosis.

Conclusion and recommendations

As diagnostic performance of GI symptoms reported to be associated with lactose malabsorption was highly variable and as primary care studies were lacking, we were unable to draw firm conclusions for clinical practice. Given the inconsistent diagnostic results of self-reported milk intolerance, our review provides no evidence that patients with self-reported milk intolerance should all be prescribed a lactose-restricted diet. High-quality studies on the diagnosis of lactose malabsorption and intolerance in primary care are clearly needed. The study population should consist of patients who consult their primary care physician for GI symptoms, regularly use milk products and for whom no strong clinical suspicion exists for other organic diseases (such as colorectal cancer, inflammatory

bowel disease, etc.). Inclusion of healthy controls is not useful if results are to be relevant to clinical practice. Such a study will result in less favourable, but much more realistic values for a test's specificity, and positive and negative predictive values. An important prerequisite of the study would be to clearly define the concept of lactose intolerance (e.g. a positive LHBT result plus accompanying clinical symptoms), as well as how it should be assessed. Only then clinically relevant research questions for which evidence is highly needed, can be studied, such as 'Which pre-test GI symptoms are useful in diagnosing lactose intolerance?'.

Acknowledgements

We would like to express our gratitude to Dr F. Fernández-Bañares, Dr J.O. Hunter and Dr A.T. Prevost, Dr F. Casellas, Prof. Dr P. Farup and Dr U.C. Ghoshal who provided us with additional diagnostic data. We thank our librarian Ingrid Riphagen for her advice on the search strategy.

Funding

ZonMw 945-06-001.

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