

Review Article

Prevalence, cause and diagnosis of lactose intolerance in children aged 1–5 years: a systematic review of 1995–2015 literature

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Background and Objectives: To assess the prevalence, etiology, diagnosis of primary and secondary lactose intolerance (LI), including age of onset, among children 1-5 years of age. Suspected/perceived lactose intolerance can lead to dietary restrictions which may increase risk of future health issues. **Methods and Study Design:** MEDLINE, CAB Abstract, and Embase were searched for articles published from January 1995-June 2015 related to lactose intolerance in young children. Authors independently screened titles/abstracts, full text articles, for eligibility against a priori inclusion/exclusion criteria. Two reviewers extracted data and assessed quality of the included studies. **Results:** The search identified 579 articles; 20 studies, the majority of which were cross-sectional, were included in the qualitative synthesis. Few studies reported prevalence of primary LI in children aged 1-5 years; those that did reported a range between 0-17.9%. Prevalence of secondary LI was 0-19%. Hydrogen breath test was the most common method used to diagnose LI. None of the included studies reported age of onset of primary LI. **Conclusions:** There is limited recent evidence on the prevalence of LI in this age group. The low number of studies and wide range of methodologies used to diagnose LI means that comparison and interpretation, particularly of geographical trends, is compromised. Current understanding appears to rely on data generated in the 1960/70s, with varied qualities of evidence. New, high quality studies are necessary to understand the true prevalence of LI. This review is registered with the International Prospective Register for Systematic Reviews (PROSPERO).

Key Words: primary lactose intolerance, secondary lactose intolerance, hydrogen breath test, prevalence, children

INTRODUCTION

Lactose is the primary digestible carbohydrate found in mammalian milk, including human milk. Physiologically, the disaccharide lactose cannot be absorbed by the intestine and needs to be enzymatically cleaved by lactase into its monosaccharides, glucose and galactose. Lactase is located at the brush border of the small intestinal villi; age related decreases in lactase activity can be a physiological phenomenon but when the decreases are a result of small intestinal mucosal damage, they can be of clinical relevance.

Lactose malabsorption is attributable to the relative imbalance between available lactase activity and ingested quantity of lactose. Undigested lactose is fermented by colonic bacteria. The result of lactose malabsorption is lactose intolerance (LI), a clinical syndrome that includes a combination of symptoms such as abdominal pain, diarrhoea, nausea, flatulence, and bloating after ingestion of lactose-containing foods.

Lactase deficiency may be primary or secondary. Congenital lactase deficiency is extremely rare. Expression of

this brush border enzyme is highly relevant for energy utilization from human milk and expression levels at birth are sufficient to adequately digest the lactose found in human milk.¹⁻⁴ Primary LI, or more correctly lactase non-persistence, is also referred to as hereditary lactase deficiency, or adult-type hypolactasia; it is genetic, irreversible, and usually develops during childhood. Secondary LI is the result of an underlying intestinal mucosal insult which results in lactase deficiency and lactose malabsorption. It can occur at any age, is mostly transient, and can result from any small intestinal injury. The incidence of secondary LI depends on the incidence of the primary ca-

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use of the injury e.g., infectious diarrhoea in young children.

In brief, several diagnostic methods are commonly used for the diagnosis of LI. The diagnosis of LI based on self-reported clinical symptoms after lactose consumption has been shown to be unreliable, due to poor correlation of the occurrence of subjective symptoms and objective methods such as the hydrogen breath test (HBT).⁵⁻⁸ The HBT is based on the generation of hydrogen during the bacterial fermentation of lactose. Hydrogen can diffuse across the gut barrier, enter the circulation, and be subsequently exhaled and detectable in the breath. HBT is conducted following administration of either lactose or milk. It has been reported that some lactose intolerant individuals may produce false negative readings in an HBT test due to absence of lactose fermenting organisms.^{9,10} Prior to the development of the HBT, the lactose tolerance test was one of the first methods to test for LI. In essence it is based on the increase of blood glucose after ingestion of lactose.¹¹ However, this test is considered to lack sensitivity and deliver false positive results due to the physiological insulin response to glucose. Genetic tests have the potential to detect alleles that are associated with lactase persistence, but do not cover all polymorphisms.¹²⁻¹⁵ It is also costly to perform and is not commonly done. Lactase activity can also be measured directly from small intestinal biopsies, though the expression of the enzyme might not be homogenous across the epithelium.¹⁶ In addition, it is invasive and assaying of the lactase activities is not widely available in many service laboratories. Reducing substances in stool and urinary lactose:lactulose ratio are also commonly used tests. However, inappropriate stool collection may make results of reducing substances inaccurate. Verbal reporting of symptoms, by either caregivers or patients themselves, is an easier though less robust measure. There is no “gold standard” test or diagnostic conditions for LI; thus, a combination of the above tests has been suggested to be most reliable, though more invasive and costly.¹⁷⁻²⁰

Studies designed to determine the incidence of LI in distinct populations and studies that describe incidence data, though they were designed for a different primary outcome, differ broadly in their use of the aforementioned diagnostic methods. Accordingly, reports on the incidence of primary and secondary LI may also differ significantly, even within global regions and ethnicities. Whilst the relevance of using the phrase “lactose intolerance” as a descriptor has been questioned,²¹ understanding the incidence of lactose non-persistence is not only relevant from an epidemiological perspective, but also from a nutritional and public health care view. Suspected/perceived LI, or the diagnosis of LI without reliable methods, leads to obvious dietary restrictions and may significantly reduce the consumption of lactose-rich dairy products, especially milk,²² which in turn would significantly reduce calcium intake. A reduction in calcium intake has been associated with an increased risk for developing osteoporosis,²³ cardiovascular disease,²⁴ and stroke.²⁵ A recent publication in an adult population showed that individuals with perceived lactose intolerance restricted themselves from dairy products which led to lower quality of life.²⁶

Dairy products have become increasingly accessible

and valued for their nutritional relevance including in areas where the population is mainly lactase non-persistent. The information on the age of onset of clinical symptoms and rate of progression from full infantile lactase capacity to complete lack of intestinal lactase capacity are important. These insights will allow public health authorities to incorporate it in their recommendations. In formulated foods e.g., for (young) children, lactose is considered a preferential carbohydrate; more desirable than the much sweeter sucrose or fructose, and having a lower glycemic index compared to those of glucose or maltose.²⁷

The aim of this systematic review is thus to answer the following research questions:

1. What is the prevalence of primary and secondary LI among children 1-5 years of age in different populations around the world?
2. What is the age of onset of primary LI in specific populations?
3. What are the causes for secondary LI in children 1-5 years?
4. How is the diagnosis of primary or secondary LI established?

METHODS

Search strategy

The literature search included studies written in English and published between January 1995 and June 2015. Three electronic databases (MEDLINE, CAB Abstract, and Embase) were searched. The following search string was used:

(lactose NEAR intoleran*) or (lactose NEAR malabsor*) OR (lactose NEAR indigest*) OR (hypolactasia OR “lactase persisten*” OR “lactase non-persisten*”) AND (infant OR infants OR infancy OR newborn OR newborns OR baby OR babies OR toddler* OR child OR children) AND (frequen* OR prevalan* OR incidence OR incident OR onset OR start OR beginning OR cause OR reason OR root OR stimulus OR stimuli OR diagnosis OR diagnostic OR detect OR detection OR identification OR identify OR discovery OR discover OR determine OR determination)

Study selection

Figure 1 illustrates the study selection process using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. We used a two stage process of exclusion when screening articles on title and abstract. The first was conducted using the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI) Reviewer; articles that contained the keywords “fever OR colchicine OR chemically-induced diarrhea* OR parenteral nutrition OR cancer OR chemotherapy OR pesticides OR systematic inflammatory disease OR chronic disease* OR animal studies OR adult OR osteoporosis OR malnourished OR Kwashiorkor OR celiac disease OR starch intolerance OR school-aged children OR veterinary medicine OR pregnancy” in the title or abstract were excluded.

Inclusion and exclusion criteria were developed a priori following extensive discussion with all authors. Articles were included if they: specifically addressed LI in in-

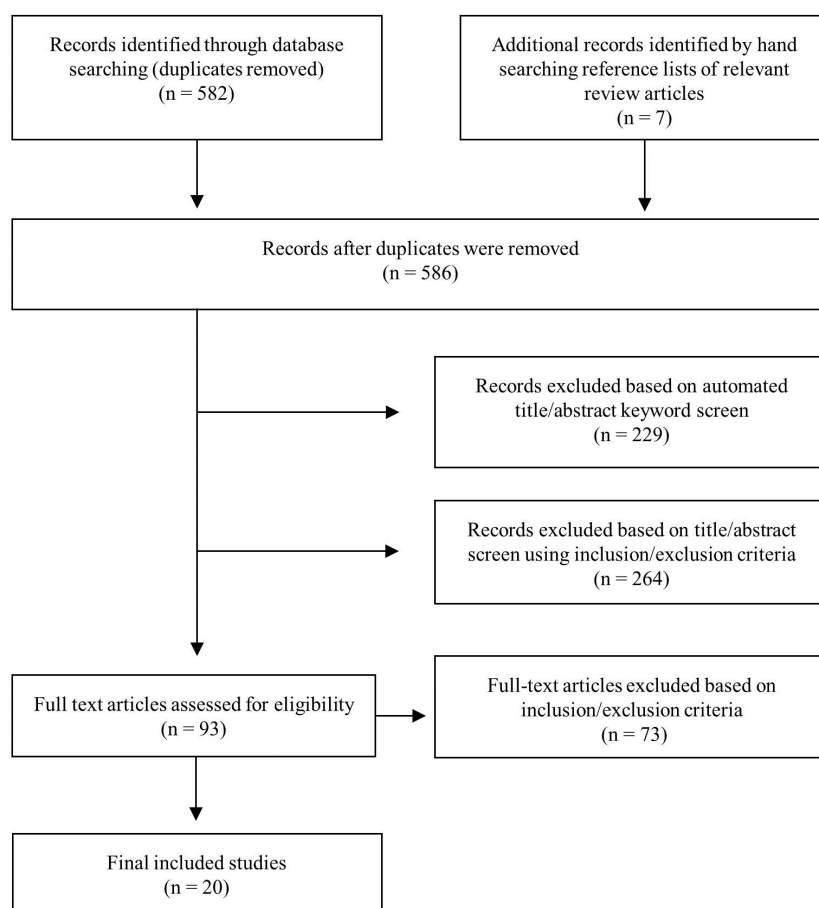


Figure 1. Flow chart of the systematic literature search and study selection process.

infants/children 1-5 years of age, genetic risk, prevalence/incidence, timing of diagnosis, method of diagnosis, effects and symptoms, or relationship to dietary patterns; focused on consumption of cow's milk and related issues including cow's milk protein allergy (CPMA), and gastrointestinal symptoms; mentioned transient or secondary LI, or referred to LI as being a potential cause or component of other plausibly related diseases, disorders or symptoms (e.g., colic, gastrointestinal infections). Articles were excluded if the age range was outside of research questions (for title/abstract screening, must be 0-5 years, for full text screening, article was excluded if the age range was only >4 years or if age range was restricted to 0-1 years); population was pre-term (infants with gestation age <37 week); focused on treatment or management of LI (including pre/pro-biotics and guidelines for feeding); focused on "implausible" relationship to other diseases (e.g., hypothyroidism); or did not appear to address LI in any manner (e.g., focused on unrelated/general food allergies, intolerances, sensitivities, or other identified issues with milk/milk abstinence etc.). All preclinical studies, case studies, non-English publications, and non-peer reviewed publications were also excluded.

Three reviewers (LH, LM, TL) independently screened titles and abstracts for eligibility against the inclusion/exclusion criteria. Two reviewers (LH and LM) then screened the remaining articles on full text based on the inclusion/exclusion criteria. Discrepancies between decisions were resolved by a third reviewer (TL). References from relevant reviews were searched to identify articles

that were not detected by the original search strategy.

Data extraction

Two reviewers (LH, LM) independently extracted the data, with each reviewer double checking the other's work. Disagreements were resolved following a discussion between both reviewers. The following data was extracted from the included studies: type of study; country of participating study sites; age range and mean age of the participants; ethnicity; sample size; objective of the study; whether participants had primary or secondary LI; method/s of diagnosing LI; pre-test conditions; specificity and sensitivity of the diagnostic methods; prevalence of LI (primary and secondary) in the overall study population and in specified/relevant sub-populations; age of onset of primary LI; symptoms of LI; and the proposed/hypothesized causes of secondary LI.

Quality assessment

The quality assessment of observational, and/or qualitative studies proved to be challenging; there is no consensus on a standardized tool to evaluate bias and quality and inappropriate usage of common checklists have been reported.^{28,29} However, assessing the quality of the body of evidence as a whole is necessary in order to interpret the review's findings. Thus, the Critical Appraisal Skills Programme Checklist (CASP) for Qualitative Research (www.casp-uk.net) was used to guide the assessment of quality of included studies. Collaboratively, three reviewers (LM, LH, AH) assessed each included article against

the CASP criteria, recording whether the article did not address the issue, partially addressed the issue, fully addressed the issue, or whether it was not possible to comment on the issue given the information provided in the article. This assessment provided a semi-quantitative approach to assessing the quality and risk of bias of the included articles.

This review has been registered with the International Prospective Register for Systematic Reviews (PROSPERO), registration number CRD42015027202.

RESULTS

Search results

The search strategy identified 579 articles. An additional seven articles were identified by hand-searching the reference lists of relevant review articles. After both automated and mechanical screening of title and abstracts using defined inclusion and exclusion criteria, 93 articles were obtained for full text screening using the same criteria. In total, 20 studies were included in the qualitative synthesis (Figure 1). The details of these included studies are described in Appendix 1a and 1b.

Included studies characteristics

The majority of included studies were cross-sectional (75%). Twelve studies were conducted in Europe, one in the United States of America (USA), five in Asia, and two in Australia. Many studies did not specify the ethnicity of the participants. Three studies focused on the methodology used to diagnose LI. Of the twenty included articles, six focused on the diagnosis of primary LI in generally healthy populations,³⁰⁻³⁵ nine discussed secondary LI,³⁶⁻⁴⁴ two captured populations that were most likely experiencing both primary and secondary LI,^{45,46} and three articles which did not specify the type of LI they assessed and used populations that were referred for HBTs during gastrointestinal and abdominal symptoms (Table 1, Appendix 1a).⁴⁷⁻⁴⁹

Prevalence and age of onset of primary LI

Six included articles focused on primary LI (Appendix 1a), however, only three included prevalence information specifically in our age range of interest (1-5 years)^{30,32,35} (Table 1). Due to the low number of studies, information

from Marek et al,³¹ with an age range of <3 years (Table 1) was also included. The prevalence of primary LI diagnosed using HBT varied from 0-16.7%. One study used two different techniques to diagnose LI, reporting two different prevalences: primary LI prevalence using an HBT was 0% whilst primary LI prevalence using a lactose tolerance test was 17.9% (Table 1).³¹ None of the included studies that reported prevalence of primary LI included information about the age of onset.

Diagnostic methods to establish primary LI

HBT was the technique most frequently used to diagnose primary LI among healthy children of 1-5 years of age (Figure 2, Appendix 1b). Dosages differed minimally, with most studies using 2 g lactose per kg body weight, to a maximum of 50 g (Appendix 1b). The lactose solution varied between 10-20% (weight per volume).

Whilst dosages were similar, there was considerable variation in the criteria or cut-off each study used to establish a diagnosis of primary LI (Appendix 1b). One study diagnosed LI only when two or more clinical symptoms were present after the ingestion of either 25 g lactose or 50 g milk powder.³⁵ Three studies reported lactose malabsorption (LM) instead of LI.^{30,32,50} Leis et al diagnosed LM as any increase in breath hydrogen of >20 ppm following 2 g/kg lactose,³⁰ whilst Myo et al diagnosed LM as peak breath hydrogen >10 ppm following the same dose of lactose.³² Alternatively, Tormo et al diagnosed LM by an increase in breath hydrogen >25 ppm after ingestion of 250 mL of cow's milk.³³ One study used the ratio of urinary lactose:lactulose ratio (with a cut-off of >0.4) as a method to diagnose lactose maldigestion.⁴⁵

Two studies included in this review further differentiated LI from milk intolerance. Yang et al. administered a milk tolerance test if a participant was diagnosed with a lactase deficiency (using HBT),³⁵ whilst Leis et al provided 250 mL milk with 12 g lactose or 250 mL of yoghurt with 10 g of lactose to those participants with positive HBTs.³⁰

Prevalence, aetiology and age of onset of secondary LI/unknown LI

In total 14 included articles discussed secondary LI or LI of unknown origin (Appendix 1a, b). Less than half of

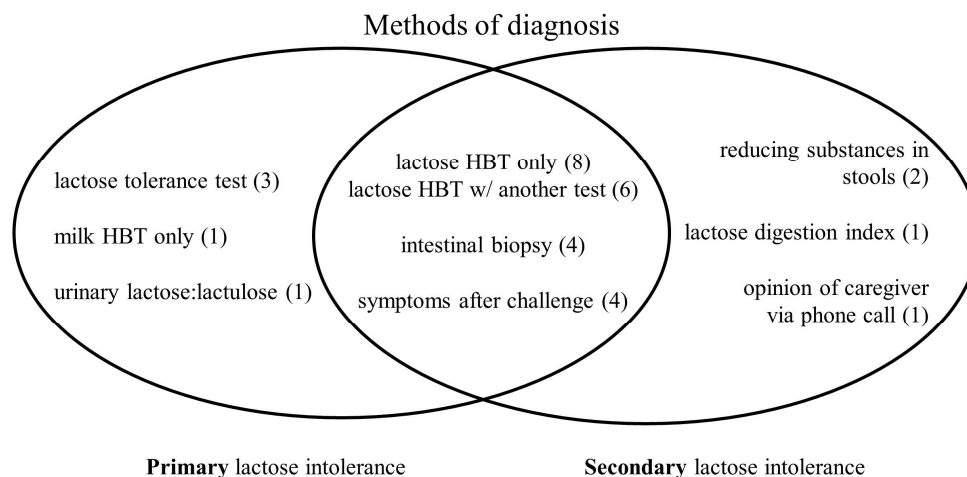


Figure 2. Frequency of use of individual methods to diagnose primary and secondary lactose intolerance.

Table 1. Prevalence of lactose intolerance (LI) among children 1–5 years of age worldwide 1995–2015

Article identifier	Age range	n	Country	Diagnostic criteria	Dosage	Type of LI [¶]	Prevalence of LI	Proposed causes of secondary LI
Leis 199 ³⁰	3–5 years	95	Spain	Lactose HBT >20 ppm	Lactose 2 g/kg (max 50 g)	Primary	9.5%	NA
Myo 1999 ³²	1–3 years	NR	Myanmar	Lactose HBT >10 ppm	Lactose 2 g/kg (max 50 g)	Primary	16.7%	NA
Yang 2000 ³⁵	3–5 years	387	China	Lactose or milk HBT >20 ppm	Lactose (25 g in 200 mL of water) or milk powder (50 g) with 13–14 g lactose	Primary	12.2%	NA
Marek 1998 ³¹	< 3 years [§]	40	Poland	Lactose HBT >20 ppm Abnormal lactose tolerance test	Lactose 1.75 g/kg (max 50g)	Primary	0% 17.9%	NA NA
Däbritz 2014 ⁴⁴	3–5 years	23	Germany	Lactose HBT >20 ppm	Lactose 1 g/kg (max 50 g)	Secondary	19%	
Wang 1998 ³⁷	13–22 months	218	UK	Sucrase:lactase activity >10	NA (intestinal biopsy)	Secondary	0%	ND
Wang 1998 ³⁷	23–60 months	264	UK	Sucrase:lactase activity >10	NA (intestinal biopsy)	Secondary	0.76%	ND
Szajewska 1997 ³⁶	0–3 years [§]	107	Poland	Reducing substances in stool, low stool pH & on milk formula	NA	Secondary	11.2%	Rotavirus
Gonzalez-Galan 2011 ⁴³	< 5 years [§]	2375	Spain	Opinion of caregiver via phone call, criteria ND	NA (phone call)	Secondary	Norovirus: 3.4% Rotavirus: 16.8%	Norovirus or rotavirus
Quak and Wong 1997 ⁴⁸	12 months to 3 years	41 [†]	Singapore	Lactose HBT ≥20 ppm Abnormal lactose tolerance test	Lactose 2 g/kg (max 50 g)	Unknown, population referred for HBT	62.3%	Upper GI mucosal abnormalities
Li 2004 ⁴⁶	0–5 years [§]	40	USA	Lactose HBT >10 ppm	Lactose 2 g/kg (max 50 g)	Unknown, population referred for HBT	48%	ND
Jones 2011 ⁴⁷	3–5 years [‡]	NR	Australia	HBT, criteria ND	Lactose 2 g/kg (max 20 g)	Unknown, population referred for HBT	19%	ND

HBT: hydrogen breath test; LI: lactose intolerance; max: maximum; NA: not applicable; ND: none described; NR: not reported.

[†]Calculated from information provided in article.

[‡]Derived from information included in article.

[§]The age range of this study is technically outside the age range of our inclusion criteria, as it includes children younger than 12 months.

[¶]Assignment of primary LI not explicitly indicated by authors but attributed by reviewers based on reported selection/inclusion criteria (e.g., healthy children).

these articles included specific information about prevalence in children 1-5 years of age. For this reason, data from three studies whose age range also included infants from 0-1 year were included.^{36,43,46} To ensure clarity and ease of interpretation of the prevalence data, data from studies with age ranges greater than 5 years of age, which did not split the prevalence according to age, are not included in Table 1. The prevalence of secondary LI varied from 0-19%, whereas the prevalence of LI of unknown origin, in populations referred for HBTs, ranged from 19-62.3%.

Information about the age of onset of secondary LI was lacking in the included articles (Appendix 1b). Only one article subdivided data in such a way to draw conclusions about age of onset; the authors show that in their population (catchment area: 40% Northern European, 5% Southern European, 30% Indian, 20% Afro-Caribbean, 5% other) the majority of LI cases were diagnosed in children older than 5 years.³⁷

The causes of secondary LI/LI of unknown origin reported in the included studies (Appendix 1b) were acute gastroenteritis (Europe),^{36,43} infections (Malaysia; Nepal, Poland),^{36,41,45} celiac disease (UK),³⁹ cystic fibrosis (Australia),⁴⁹ and cow's milk allergy (Italy).⁴⁰ Other studies included results from children who had small bowel biopsies due to undisclosed reasons (Netherlands),^{38,42} undisclosed referrals for HBTs (US, UK),^{37,46} and recurrent abdominal pain/gastrointestinal symptoms (Germany, Singapore, Australia).^{39,42,43}

Diagnostic methods to establish secondary LI

There was a large variety of techniques used to diagnose secondary LI or LI of unknown origin (Figure 2, Appendix 1b). Among studies assessing acute gastroenteritis as the primary aetiology of LI, two of the four studies used reducing substances in stools as a diagnostic method, using a cut-off of >0.5% with or without stool pH criteria.^{36,41} One study assessed children with chronic diarrhoea (diarrhoea for >14 days) and failure to thrive and diagnosed secondary LI by measuring lactase and sucrase activity in intestinal biopsy samples.³⁷ A positive diagnosis of secondary LI was made when the sucrase:lactase ratio was >10.³⁷

Two of the included studies (Appendix 1b) used relatively unconventional methods to establish secondary LI.^{35,38} A Spanish study in children with acute gastroenteritis established diagnoses of secondary LI based on reports from caregiver/s during follow-up telephone calls.⁴³ In Italy, among children with cow's milk allergy, the diagnosis was established after either onset of symptoms or a negative response following the fourth dose of a cow's milk or lactose challenge.⁴⁰ This was the only included study to conduct a dose-response test to diagnose LI. Neither study discussed or reported the validation of these methods.

Among other conditions, including children who had undergone a small bowel biopsy, had recurrent abdominal pain or were referred for HBTs, lactose HBTs were the most common diagnostic method. However, the concentration of lactose used varied between solutions of 10-20% (weight per volume), with dosages from 1-2 g/kg, and maximal dosages of 20 or 50 g. The cut-off for estab-

lishing LI was similar, with increased hydrogen levels >20 ppm from baseline. However the time points for evaluation differed, from either a single time point, to a positive diagnosis requiring at least three consecutive positive samples.

Quality of included studies

Overall, according to our application of the CASP criteria, the quality of nearly half of the included studies was low. Many studies had a very low number of participants, with only four studies having an n of over 1000 (Appendix 1a). Almost all of the studies did not consider or address the relationship between the participant and the researcher, and many did not fully explain whether the study protocol was registered and approved by an ethics board, or the technique used to recruit and enrol the participants in the studies. In addition, data analyses in many of the included papers were not sufficiently rigorous, or described within the Methods section. Examples of high quality included studies were Leis et al 1997, Myo et al 1999, Yang et al 2003, Szajewska et al 1992, Lee et al 2003, Goto et al 2002, Li et al 2004, Jones et al 2011 and Quak et al 1997.^{25,27,30,31,36,40-43}

DISCUSSION

To accurately assess the state of current knowledge, relatively narrow date range (1995 – 2015), age range (1-5 years) and search terms (i.e., (lactose NEAR intoleran*) or (lactose NEAR malabsor*) OR (lactose NEAR indigest*) were used for this review. This limited inclusion of studies among children with wider age ranges (e.g., studies which included children older than five years of age or that included both children and adults in the study)^{51,52} and studies which assessed similar topics using different nomenclature (e.g., use the term “carbohydrate” vs “lactose” intolerance).⁵³ In essence, few studies assessing LI in young children have been published in the last 20 years. It is evident from the reference lists of many of the included articles and narrative reviews on the topic that current understanding of the prevalence of LI in children 1-5 years of age relies heavily on data generated in the 1960s and 1970s. This review is most likely the first to highlight the paucity of current literature on LI in young children.

The age of onset nor the geographical differences in prevalence of primary LI could not be established from the four studies included in this review. Recent data, published after this literature search, showed that the prevalence of primary LI among older Indonesian children (3-5 years of age) was 21.3%,⁵⁴ whilst the only included paper in this review that focused on Asian children of the same age collected during the same time period showed that the prevalence of primary LI in Chinese children was 12.2%.³⁵ This may be due to differences in diagnostic criteria used to establish incidence. Although both studies used HBT, the Indonesian study used a dose of 2 g lactose per kg body weight and measured breath hydrogen levels 60 min post lactose ingestion, whilst the Chinese study administered 25 g lactose in 200 mL water and measured breath hydrogens level 180 min post ingestion. Thus, titration of dosage according to size of participants and standardisation the timing of breath hydrogen as-

assessment may be key components in standardizing methodologies between countries, to allow for essential geographical comparisons.

These geographical comparisons are important as there is a persisting perception that LI is more prevalent in children of Asian ethnicity compared to Caucasian children. This stereotype may be due to the known population differences in prevalence of lactase persistence in adults. Lactase persistence describes the continued post-weaning production of lactase that allows humans to continue digesting lactose throughout adulthood. Some populations in Europe and Africa exhibit high prevalence of lactase persistence, whereas many Central and East Asian populations do not.^{55,56} It has been hypothesized that the absence of lactose in Asian diets did not favour lactase persistence beyond childhood. A recent publication argued that non-lactase persisters could still be lactose tolerant and questioned whether the terminology “lactose intolerance” was adequate.⁵⁷

Though these findings are derived from adult data, the findings are often extrapolated and applied to infants and children. This can lead to the emergence of perceived LI, as parents self-diagnose children, rather than well-established diagnosed LI. This discrepancy can have consequences as unnecessary dietary restrictions may be applied to “manage” the perceived LI. The lack of insight on age of onset of primary LI from the included literature in our review highlights the lack of recent information about this phenomenon.

The differences in methodology and diagnostic criteria used in the included studies in this review may be due to the fact that there is no worldwide “gold standard” to diagnose lactose intolerance.^{17,19,20,58} Currently, the most well-accepted and standardized test is the HBT and indeed, among the included studies, HBT was the most commonly used method to diagnose primary and secondary LI. Of the included studies that included prevalence data within our specified age range (Table 1), all that assessed primary LI used lactose HBT as a diagnostic tool, whereas only one study out of the five that assessed secondary LI used this technique. Thus, confidence in the reporting of the prevalence of primary LI is high, whilst the reported prevalence of secondary LI is open for interpretation and critique. Yet the use of “standardized” methods is no guarantee of consistency in diagnosis; for example Marek et al. described a prevalence of primary LI of 0% using HBT (1.75 g/kg in 15-20% solution, maximum 50 g) but a prevalence of 17.9% following a subsequent lactose tolerance test which assessed lactose level in the blood.⁵⁹ Establishing diagnoses based on invalidated methods, such as report from caregivers during follow-up telephone calls or after a negative response following the fourth dose of milk challenge, further complicates interpretation of the studies. The dose of lactose used to induce a response was relatively homogeneous, varying between 1.75 g and 2 g per kg body weight whilst the maximum dose varied between 20-50 g, driven by the age range/size of the participants. The most frequently used diagnostic cut-off for LI using HBT was 20 ppm above baseline. However, the timing for this increment varied from two consecutive measures within 30 min to any two different points during the study. In addition, the terms

“lactose intolerance” and “lactose maldigestion” (which refers to an inability to hydrolyse lactose) were used interchangeably in many studies, making it difficult to compare prevalence data.

Most HBTs in the included studies used pure lactose as the challenge agent. This is a methodological issue, as lactose is rarely consumed in isolation and is otherwise incorporated in a food matrix. Thus, a more appropriate test could be the dairy food tolerance (DFT) test which establishes the level of tolerance of lactose in a certain food, as opposed to lactose intolerance.²¹ In the DFT test, lactose tolerance levels are derived from a chosen lactose-containing product, which is standardised against a reference of 250 mL of ultra-heat treated full fat liquid milk.²¹ This may determine a more accurate tolerance level for each product, tested at an appropriate serving size, and in an appropriate cultural context, as compared to testing 50 g of lactose which would not normally be found in one serving of a particular food and may not reflect local food culture.²¹

Though an association between secondary LI and infectious diarrhoea has been suspected, the epidemiological data to substantiate this link is surprisingly scarce. A review on the global burden of childhood pneumonia and diarrhoea estimated that in 2010 there were 1,731 billion episodes of diarrhoea in children younger than five years.⁶⁰ The same review concluded that, from a worldwide perspective, Asia and Africa had the highest incidence and severity burden for these diseases. Yet, none of the four included studies that explicitly reported secondary LI (Table 1) were performed in these regions. A Thai study investigating carbohydrate intolerance in outpatients experiencing infantile diarrhoea described an incidence of secondary carbohydrate intolerance of 31.5%, which is similar to findings reported in this review.⁵³

Understanding LI prevalence is quite important as it could affect dietary habits of a child. The latest international expert recommendations for young child formula (YCF) advised that lactose content for products for this age group should be at least 50% of total carbohydrate.⁶¹ Whole cow's milk contains approximately 12.8 g of lactose per 200 mL,⁵⁸ and 50% of lactose in one glass of YCF with energy density of 70 kcal/100 mL should be equal to at least 6.3 g per 200 mL.⁶¹ Taking into account that LI symptoms may not be prominent if less than 25 g per day is consumed, a child with LI may still drink 1-2 glasses of cow's milk or 1-3 glasses of YCF per day, without reporting symptoms, in order to improve calcium intake and absorption. However, this tolerance level could be lower in those with chronic abdominal pain⁶² or in those with perceived LI rather than actual LI. In these products, substituting lactose with lower quality carbohydrates and without adapting the level of several nutrients, including calcium and phosphorus could potentially hamper optimal intestinal calcium absorption and thus increase the risk for osteoporosis.^{63,64} There is also a need to consider subjective symptoms when assessing lactose tolerance as the clinical manifestation in lactase non-persistent subjects could be different due to differences in lactase fermentation by the colonic microbiota between individuals.⁶⁵

Conclusion

There is little recent literature capturing the prevalence of primary and secondary LI in children aged 1-5 years. The majority of studies use lactose HBT to diagnose LI; the ranges of prevalence of primary LI (0-17.9%) and secondary LI (0-19%) are very similar, with no obvious regional differences. The studies included in this review state diverse causes for secondary LI, ranging from infectious diarrhoea to celiac disease. New, high quality studies with well standardised diagnostic methods, such as the DFT test, are necessary to accurately understand the true prevalence of primary and secondary LI, or lactose non-persistence, in young children across regions. It is also important to establish the tolerance level of commonly consumed lactose-containing food in order to avoid unnecessary dietary restrictions which may lead to increased health risks.

AUTHOR DISCLOSURES

LM, LH, AH and JB are employee of Danone Nutricia Research, Singapore. TL is an employee of Nutricia Research, Utrecht, the Netherlands.

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Appendix 1A. Overview of studies included in the systematic review

First author	Year	Type of study	Primary objective	Primary or secondary lactose intolerance	Study population	Time of data collection	Country	Ethnicity	Overall age range (incl. mean if stated)	Overall sample size	Age range relevant to review (incl. mean/median if stated)	Sample size of relevant age range
Leis ³⁰	1997	Single center, cross-sectional	To evaluate the prevalence of lactase malabsorption in Galicia, Spain	Primary	General population	ND	Spain	ND	3–85 years	850	3–5 years	95
Quak and Wong ⁴⁸	1997	Single center, cross-sectional	To determine the prevalence of LI and upper gastrointestinal mucosal pathology in a group of children with recurrent abdominal pain	Unknown	Children who complain of intermittent abdominal pain of unexplained origin for more than 3 months duration	ND	Singapore	89.6% Chinese, 6.6% Indian, 3.8% Malay	0–12+ years (eldest child: 18 year)	183	Data provided by year of age, so can calculate data for 1–5 years	33 [†]
Szajewska ³⁶	1997	Single center, cross-sectional	Determine the prevalence of carbohydrate intolerance in Polish children during an acute episode of diarrhoea	Secondary	Children submitted to hospital with acute gastroenteritis i.e., an onset of water or extremely loose stools with or without vomiting for at least 1 but less than 5 days	Sep 1995–Mar 1996	Poland	ND	0–3 years (12.5 months)	107	12 months to 3 years	41 [†]
Lewindon ⁴⁹	1998	Single center	To describe the frequency of lactose malabsorption in a paediatric CF population referred for investigation of abnormal bowel function	Unknown	Pediatric patients CF and non-CF with gastrointestinal disturbance	Since 1981 (no end date described)	Australia	ND	1 month to 19 years	4812	Data not subdivided	NA
Marek ³¹	1998	Cross sectional	To compare the usefulness of LTT and HBT for the diagnosis of lactose intolerance in children	Primary	Suspected lactose intolerance	ND	Poland	ND	4 months to 15 years	113	4 months to 3 years	40

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy.

[†]Calculated from data provided in the article.

Appendix 1A. Overview of studies included in the systematic review (cont.)

First author	Year	Type of study	Primary objective	Primary or secondary lactose intolerance	Study population	Time of data collection	Country	Ethnicity	Overall age range (incl. mean if stated)	Overall sample size	Age range relevant to review (incl. mean/median if stated)	Sample size of relevant age range
Wang ³⁷	1998	Retrospective and prospective (review will focus on retrospective)	To investigate the onset of expression of a polymorphism on lactase gene in children.	Secondary	Patients in whom a temporary GI disorder had resolved, a possible diagnosis of celiac was excluded and no GI cause was found for symptoms	ND	United Kingdom	Catchment area is ~40% N. European, 30% Indian, 20% Afro-Caribbean, 5% S. European, 5% Other	2 months to 11 years	866	I: 13–22 months II: 23–60 months	I=218 II=264
Koetse ³⁸	1999	Single center, cross sectional	To test the new ¹³ C-lactose breath test in paediatric patients	Secondary	Patients who had undergone a small bowel biopsy	ND	Netherlands	ND	11 months to 19 years	27	Data not subdivided	NA
Myo ³²	1999	Single center, cross sectional	To determine the prevalence of lactose malabsorption in Myanmar children	Primary	General child population	ND	Myanmar	ND	1–12 years (5.4 years)	125	1–3 years	ND
Yang ³⁵	2000	Multi-center, cross sectional	To determine lactose metabolism and lactase activity as well as prevalence of lactase deficiency and lactose intolerance in Chinese children of different ages	Primary	General child population	Sep-Dec 1997	China	Chinese	3–13 years	1168	3–5 years (4.5±0.78)	387
Tormo ³³	2001	Single center, cross-sectional	To study the pattern of methane production in normal conditions and in lactose malabsorption	Primary	General population and lactose malabsorbers	ND	Spain	ND	General population: 0–9 years Lactose malabsorbers: 0–18 months	365	12–18 months	ND

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy.

[†]Calculated from data provided in the article.

Appendix 1A. Overview of studies included in the systematic review (cont.)

First author	Year	Type of study	Primary objective	Primary or secondary lactose intolerance	Study population	Time of data collection	Country	Ethnicity	Overall age range (incl. mean if stated)	Overall sample size	Age range relevant to review (incl. mean/median if stated)	Sample size of relevant age range
Goto ⁴⁵	2002	Single center, cross-sectional	To determine the relationship between intestinal permeability, growth status, weaning practices, parasite infection and reported morbidity in children 0–60 months old	Both (Primary and Secondary)	General child population	Sep 1999-Apr 2000	Nepal	Tibeto-Burmese, Indo-Aryan high caste and Indo-Aryan low caste	0–5 years	210	Data not subdivided	NA
Murphy ³⁹	2002	Single center, cross-sectional	To determine the utility of the lactose H ₂ breath test as a non-invasive technique for testing lactose malabsorption that can occur in untreated celiac disease	Secondary	Children with celiac disease	ND	United Kingdom	82% Caucasian, 18% South Asian	0.9–14.75 years (median 3.2 years)	44	Data not subdivided	NA
Fiocchi ⁴⁰	2003	Single center, cross-sectional (double blind, placebo controlled food challenge)	To prospectively assess clinical tolerance to lactose from bovine source in a consecutive series of 24 children with CMA	Secondary	Children with cow milk allergy	Jun 1-Dec 31, 2001	Italy	ND	2 months–8.9 years	26	Data not subdivided	NA
Lee ⁴¹	2003	Single center, retrospective	To determine the epidemiology and morbidity of children hospitalized with rotavirus infection in a large urban hospital in Malaysia	Secondary	Children with rotavirus infection	Jan 1996-Dec 1999	Malaysia	Malay, Chinese and Indians	0 to >5 years	271	1–5 years	165
Li ⁴⁶	2004	Cross-sectional	To assess the feasibility of using an at home breath-sampling technique in patients referred for HBT	Both (Primary and Secondary)	Children referred for HBT	1996-2002	United States of America	ND	0–unstated (<5 yrs, 5–18 years, >18 years)	372	0–5 years	40

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance: lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy.

†Calculated from data provided in the article.

Appendix 1A. Overview of studies included in the systematic review (cont.)

First author	Year	Type of study	Primary objective	Primary or secondary lactose intolerance	Study population	Time of data collection	Country	Ethnicity	Overall age range (incl. mean if stated)	Overall sample size	Age range relevant to review (incl. mean/median if stated)	Sample size of relevant age range
Koetse ⁴²	2006	Single center, cross-sectional	The relation between LA measured in vitro in a SBB and in the in vivo lactose digestive capacity in children with suspected small intestinal mucosal damage	Secondary	Patients who had undergone a small bowel biopsy	ND	Netherlands	Caucasian descent	0.8–10.9 years (3.9 years)	18	Data not subdivided	NA
Wiecek ³⁴	2010	Single center, cross-sectional	To evaluate sensitivity and specificity of the HBT, oral lactose load and lactase activity using intestinal biopsy	Primary	Children who were patients due to abdominal pain and/or body mass deficiency	ND	Poland	ND	3–18 years (11 years)	61	Data not subdivided	NA
Gonzalez-Galan ⁴³	2011	Prospective, single center	Determine the impact of viral and bacterial pathogens on paediatric population suffering from acute gastroenteritis	Secondary	Children with acute gastroenteritis	Apr 1, 2006-Apr 1, 2007	Spain	ND	< 5 years	2375	Data not subdivided	NA
Jones ⁴⁷	2011	Single center, cross-sectional, retrospective	To evaluate whether age had an effect on the diagnosis of fructose malabsorption in a clinical setting	Unknown	Patients referred for testing for carbohydrate malabsorption as a cause of GI symptoms	2003-2008	Australia	ND	0.1–79 years	3073	Data not subdivided	NA
Däbritz ⁴⁴	2014	Single centre, cross-sectional, retrospective with 15 months of follow-up	To review HBT results and the occurrence of carbohydrate malabsorption in paediatric patients	Secondary	Population experiencing recurrent abdominal symptoms, symptoms of functional bowel disorders, or chronic/recurrent abdominal pain based on Rome III criteria	Jan 2005-Aug 2010	Germany	Caucasian descent	3–18 years	206	3–5 years (4.3 years)	23

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy.

†Calculated from data provided in the article.

Appendix 1B. Overview of diagnostic methods and causes of secondary lactose intolerance

First author	Year	Pre-test conditions described	Method of diagnosis	Dosage	Diagnostic cut-off	Sensitivity of diagnosis	Symptoms	Proposed causes of secondary lactose intolerance
Leis ³⁰	1997	Yes	Lactose HBT Test A: Ingestion of a 20% aqueous solution of lactose If Test A was positive, then either Test A1, A2, B or C was administered: Test A1 25 g lactose; Test A2 12.5 g lactose; Test B 250 mL of milk (12 g lactose/250 mL); Test C 250 mL of yogurt (10 g lactose/250 mL)	Lactose 2 g/kg (max 50 g)	LM: increase of > 20 ppm H ₂ GI symptoms must be present	ND	Vomiting, nausea, diarrhoea, belching, flatulence, abdominal pain, abdominal distention	ND
Quak and Wong ⁴⁸	1997	Yes	Oral LTT or lactose HBT	Lactose 2 g/kg (max 50 g)	LTT = increase in blood glucose ≤ 2 mmol/L HBT = increase ≥ 20 ppm	ND	Recurrent abdominal pain. Of sufficient severity to affect activity and of unexplained origin for >3 months' duration. In young children, the pain was perceived by parents as severe "crying episodes" or "colic" which did not respond to conventional treatment.	Upper GI mucosal abnormalities
Szajewska ³⁶	1997	No	Reducing substances in stool	NA	Reducing substances >0.5% and pH <5, and patient was receiving milk formula	ND	Acute diarrhoea	Frequency of LI was significantly higher in children with rotavirus gastroenteritis than without.
Lewindon ⁴⁹	1998	No	Lactose HBT	Lactose 2 g/kg (max 20 g)	Corrected rise in H ₂ of ≥ 10 ppm sustained for at least two consecutive samples	ND	Chronic diarrhoea	Control population had been referred to HBT due to gastrointestinal disturbances/abnormal bowel function.
Marek ³¹	1998	Yes	Lactose HBT Lactose tolerance test	Lactose 1.75 g/kg (max 50 g)	Max Δ H ₂ ppm as either 10–20 or >20 ppm.	ND	Children <3 years: intestinal colic, vomiting, loose stools, characteristic of fermentative diarrhoea.	NA

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LM: lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy; Sens: sensitivity; Spec: specificity.

[†]Calculated from data provided in the article.

Appendix 1B. Overview of diagnostic methods and causes of secondary lactose intolerance (cont.)

First author	Year	Pre-test conditions described	Method of diagnosis	Dosage	Diagnostic cut-off	Sensitivity of diagnosis	Symptoms	Proposed causes of secondary lactose intolerance
Wang ³⁷	1998	No	Intestinal biopsy to measure lactase, sucrase and maltase activity. Activity expressed as ratio of lactase to sucrase (L/S) or sucrase to lactase (S/L)	NA	S/L ratio >10 considered diagnostic of lactase non-persistence	ND	ND	NA
Koetse ³⁸	1999	Yes	¹³ C-lactose solution HBT Lactase activity in biopsy specimens	Lactose 2 g/kg (max 50 g)	$\Delta H_2 > 20$ ppm at any time point during the test period.	HBT: sens 54%, spec 90%, CO ₂ : sens 69%, spec 70%, Combined HBT and CO ₂ : sens : 85%, spec: 65%	NA	NA
Myo ³²	1999	Yes	Lactose HBT	Lactose 2 g/kg (max 50 g)	LM = peak H ₂ ≥ 10 ppm above baseline in samples obtained 30–180 min after lactose. Non- H ₂ detection = peak H ₂ < than 10 ppm above baseline	5.6% children were non-hydrogen producers	Abdominal pain, diarrhoea, nausea, vomiting, flatulence	NA
Yang ³⁵	2000	Yes	1. Lactose HBT 2. Occurrence of symptoms If lactase deficiency, subject was given milk tolerance test every three days	Lactose (25 g in 200 mL of water) or milk powder (50 g) with 13–14 g lactose	1. Lactase deficiency = H ₂ rise of >20 ppm after a test meal of 25 g lactose or 50 g milk powder. 2. Lactose intolerance = presence of two or more clinical symptoms after ingestion of 25 g lactose or 50 g milk powder during test period	ND	Colicky pain, abdominal distension with flatulence and diarrhoea	NA
Tormo ³³	2001	No	Lactose HBT	Cow's milk (250 mL)	Test was pathologic H ₂ was over 25 ppm (after CO ₂ correction)	ND	NA	NA
Goto ⁴⁵	2002	No	Urinary lactose:lactulose	400 mg lactulose and 100 mg mannitol dissolved in 2 mL water/kg	Lactose maldigestion diagnosed with ratio of urinary lactose:lactulose >0.4	ND	Diarrhoea	Hypothesized: 54% of children whose stools were examined (173/210) had parasite infection. Of those, 59% had ascaris lumbricoides

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LM: lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy; Sens: sensitivity; Spec: specificity.

[†]Calculated from data provided in the article.

Appendix 1B. Overview of diagnostic methods and causes of secondary lactose intolerance (cont.)

First author	Year	Pre-test conditions described	Method of diagnosis	Dosage	Diagnostic cut-off	Sensitivity of diagnosis	Symptoms	Proposed causes of secondary lactose intolerance
Murphy ³⁹	2002	Yes	Lactose HBT	Lactose 2 g/kg (max 50 g)	Sustained rise in breath H ₂ of >10 ppm above fasting baseline	ND	Diarrhoea, abdominal distension, abdominal pain, vomiting, short stature, wasting, anaemia, hypalbuminaemia	Untreated celiac disease
Fiocchi ⁴⁰	2003	No	Clinical display of symptoms	16, 32, 64 and 128 mL cow's milk added to soy formula to a total volume of 240 mL. Four increasing doses of lactose, to a maximum of 11.6 g in soy formula. Placebo was soy formula.	First onset of symptoms or negative response after the fourth dose.	ND	ND	Cow's milk allergy
Lee ⁴¹	2003	No	Reducing substances in stool	Formula containing lactose (volume not described)	Recurring watery stools with reducing substances >0.5%	ND	Prolonged diarrhoea/watery stools	Rotavirus infection
Li ⁴⁶	2004	Yes	At home lactose HBT sampling via a nasal prong technique.	Lactose 2 g/kg (max 50 g)	Rise in H ₂ concentration of >10 ppm above baseline.	ND	Abdominal pain and diarrhoea	ND
Koetse ⁴²	2006	Yes	1. Lactose digestion index: ratio between the serum ¹³ C-glucose and ² H-glucose concentrations 2. Lactase activity in small bowel biopsy samples	¹³ C-lactose 2 g/kg Reference substrate, 6.6/ ² H-glucose at 0.04 g/kg	Lactose persistence if ratio of ¹³ C glucose: ² H glucose >0.45. Low lactase activity if lactase <10 U/g protein.	ND	Diarrhoea, abdominal cramps, vomiting, flatulence	Hypothesised: small intestinal mucosal damage as a result of celiac disease, IBD, or cytostatic therapy
Wiecek ³⁴	2010	No	1. Lactase activity in biopsy specimens from small intestine mucosa 2. Lactose HBT 3. Oral lactose tolerance test evaluating glucose in capillary blood 4. Clinical pictures	Lactose 1.75 g/kg (max 50 g).	1. Lactase activity determined using Dahlquist's method in Dyduch's modification 2. Rise in H ₂ concentration >20 ppm 3. Increase in glucose concentration <20 mg%	1. HBT: sens 94%, spec 45%, reliability of + results 78%, reliability of - results 71% 2. Oral lactose test: sens 85%, spec 30%, reliability of + results 74%, reliability of - results 47%	Abdominal pain, body mass deficiency, recurrent vomiting, chronic diarrhoea, constipation	NA

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LM: lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy; Sens: sensitivity; Spec: specificity.

†Calculated from data provided in the article.

Appendix 1B. Overview of diagnostic methods and causes of secondary lactose intolerance (cont.)

First author	Year	Pre-test conditions described	Method of diagnosis	Dosage	Diagnostic cut-off	Sensitivity of diagnosis	Symptoms	Proposed causes of secondary lactose intolerance
Gonzalez-Galan ⁴³	2011	No	Opinion of caregiver via phone call	NA	ND	ND	ND	Rotavirus or norovirus infection
Jones ⁴⁷	2011	Yes	Lactose HBT: for children, samples were collected by either blowing through a straw or using nasal prong	Lactose 2 g/kg (max 20 g)	ND	ND	Gastrointestinal symptoms	ND
Däbritz ⁴⁴	2014	Yes	Lactose HBT	Lactose 1 g/kg (max 50 g)	Rise in H ₂ >20 ppm and two fold increase of the individual baseline H ₂ exhalation (if baseline >10 ppm) in three consecutive samples.	ND	Abdominal pain, diarrhoea, skin blushing, nausea, constipation	ND

CF: cystic fibrosis; CMA: cow milk allergy; GI: gastrointestinal; HBT: hydrogen breath test; IBD: inflammatory bowel disease; LA: lactose absorption; LI: lactose intolerance; LM: lactose malabsorption; LTT: lactose tolerance test; NA: not applicable; ND: not described; SBB: small bowel biopsy; Sens: sensitivity; Spec: specificity.

[†]Calculated from data provided in the article.