Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis

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Summary

Background Studies have shown wide variation in the prevalence of lactose malabsorption across the world, but no systematic reviews or meta-analyses have recently assessed the prevalence of lactose malabsorption in different geographical areas. We aimed to present an updated systematic review and meta-analysis on the prevalence of lactose malabsorption in adults, by countries and regions, and to assess the variation between different testing methods.

Methods Studies reporting on prevalence of lactose malabsorption and lactase persistence were identified by searching MEDLINE and Embase from database inception to Nov 2, 2016. We evaluated studies presenting lactose malabsorption or lactase persistence prevalence data in adults and children aged 10 years or older, including cross-sectional and prospective studies, using genotyping, hydrogen breath tests, lactose tolerance tests, and other testing methods. We excluded studies in children younger than 10 years, studies using self-reported data, and studies including inpatients and outpatients at gastroenterological wards. Studies were screened by two authors (CLS and SKF) and data values were extracted by two authors (CLS and SKF) independently. The primary outcome was the prevalence of lactose malabsorption. This study is registered with PROSPERO, number CRD42017064802.

Findings We screened 2665 records, and 306 study populations from 116 full-text articles were included (primary sources); data for 144 additional study populations from 59 articles were obtained from review articles, because full-text primary articles could not be obtained (secondary sources). Of the 450 study populations included, 231 were assessed by genotyping, 83 by hydrogen breath tests, 101 by lactose tolerance tests, and 35 by other methods or methods that were not described sufficiently. The studies included 62 910 participants from 89 countries (covering 84% of the world's population). When standardising for country size, the global prevalence estimate of lactose malabsorption was 68% (95% CI 64–72), ranging from 28% (19–37) in western, southern, and northern Europe to 70% (57–83) in the Middle East. When assessing the global prevalence using genotyping data only, the estimate was 74% (69–80), whereas prevalence was 55% (46–65) using lactose tolerance test data, and 57% (46–67) using hydrogen breath test data. Risk of bias was assessed based on ten indicators; 12 of the articles had a score of ten, indicating low risk of bias, 76 had a score of nine, 26 a score of eight, and two articles a score of seven (indicating higher risk of bias). There was substantial heterogeneity between studies within most of the assessed countries.

Interpretation Lactose malabsorption is widespread in most of the world, with wide variation between different regions and an overall frequency of around two-thirds of the world's population. Acknowledging regional patterns of lactose malabsorption is important to guide management of gastrointestinal symptoms.

Funding None.

Introduction

Lactase is an enzyme that hydrolyses lactose into glucose and galactose.[1,2] This allows the intestines to absorb carbohydrates from milk—a process that is especially important in newborn babies feeding on mammalian milk. Most newborn babies have high concentrations of lactase, but concentrations decline after weaning.[3] This occurs to varying degrees across different populations, and can result in lactose malabsorption.[4] Lactose malabsorption occurs when non-hydrolysed lactose passes through the intestines without being absorbed, thus acting as a bacterial substrate in the colon and frequently causing osmotic diarrhoea. When lactose malabsorption is combined with symptoms, it is often referred to as lactose intolerance.[5] Depending both on the amount of lactose ingested and on the activity of lactase, people with lactose malabsorption can experience gastrointestinal symptoms such as diarrhoea, flatulence, nausea, gut distension, and abdominal pain, as well as more systemic symptoms such as headache.[6–8] Thus, being aware of the frequency of lactose malabsorption in different geographical areas is important both for clinicians when assessing patient symptoms, and for policy makers, for example when assessing choice of food aid in response to famines.

Lactose malabsorption has traditionally been diagnosed with lactose tolerance tests or hydrogen breath tests. In the past 10–15 years, genetic tests have often been used to evaluate lactase persistence, which is linked with better absorption of lactose. Lactase activity usually

Research in context

Evidence before this study

Most newborn babies have high concentrations of the enzyme lactase, but concentrations decline after weaning. This occurs to varying degrees across different populations, and can result in lactose malabsorption. Lactose malabsorption and intolerance can cause substantial gastrointestinal symptoms when not recognised and lactose consumption is not limited. We searched MEDLINE and Embase from database inception, to Nov 2, 2016, for studies that included lactose malabsorption prevalence data, excluding articles not published in English, German, French, Spanish, Italian, Portuguese, Norwegian, Danish, or Swedish. We also checked references from relevant reviews identified by our search. We identified 2665 records, and 306 study populations from 116 full-text articles were included (primary sources); data for 144 additional study populations from 59 articles were obtained from review articles, because full-text original articles reporting these data could not be obtained (secondary sources).

Although lactose malabsorption is widespread, studies have indicated that the frequency varies widely between and, to some extent, within geographical regions—from uncommon to nearly universal. No up-to-date systematic reviews or meta-analyses have been published on the frequency of lactose malabsorption in different geographical areas.

Added value of this study

This study provides national, regional, and global estimates on lactose malabsorption. Assessed by a combination of methods, lactose malabsorption has an estimated global prevalence of 68%. Studies using genotyping have generally reported a slightly higher frequency, whereas those using hydrogen breath tests and lactose tolerance tests report a lower frequency. Nonetheless, all methods indicate that lactose malabsorption is widespread in most of the world.

Implications of all the available evidence

Recognition of lactose malabsorption patterns is important to guide identification of likely causes of gastrointestinal symptoms and their optimal management. Furthermore, knowledge of lactose malabsorption patterns is of public health importance for guiding policy—eg, when choosing food for provision during famine outbreaks.

declines gradually during the first 10 years of life except among those with a highly conserved mutation in the promoter region of the lactase gene.[9] Several single nucleotide polymorphism (SNP) mutations in this gene are highly associated with lactase persistence.[10] The first known SNP (C/T-13910) was mostly applicable for estimating lactase persistence (and lactose malabsoption) in northern European populations, but with a gradual increase in the number of known SNPs associated with lactase persistence, genotyping is now more applicable in populations in a range of geographical settings.

Different studies have shown wide variation in the prevalence of lactose malabsorption across the world, ranging from 4% in Denmark to almost 100% in China and among native Americans.[11–13] Variation has been seen not only between countries, but also within countries. Several reviews have addressed this topic,[7,9,14,15] but to our knowledge no systematic reviews or meta-analyses have recently assessed the prevalence of lactose malabsorption in different geographical areas. One systematic review included studies published until 2009,[7] but since then many further studies have been published. Thus, our objective is to present an updated systematic review and meta-analysis on the prevalence of lactose malabsorption in different geographical areas and countries, to estimate the global burden, and to assess variation in estimates between different testing methods.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we evaluated studies presenting prevalence data of lactose malabsorption or lactase persistence, including cross-sectional and prospective studies using genotyping, hydrogen breath tests, lactose tolerance tests, or other methods.

Studies were identified by searching MEDLINE from database inception (1946) to Nov 2, 2016, and Embase from database inception (1974) to Nov 2, 2016, through the Ovid portal. No limits were applied for language in the search, but studies not published in English, German, French, Spanish, Italian, Portuguese, Norwegian, Danish, or Swedish were later excluded during screening. We also checked references from relevant reviews identified by our search.[7,9,14,15] We also made a separate table for studies assumed to be relevant that we were unable to obtain in collaboration with an experienced librarian. This systematic review and meta-analysis adheres to the PRISMA criteria.[16]

The search was initially conducted on March 16, 2016, and updated and revised on Nov 2, 2016. The search included the following terms: "lactose intolerance", "lactase deficiency, congenital", "lactose sensitivity", "carbohydrate malabsorption", "glucose-galactose malabsorption", "lactase deficiency", "alactasia", "hypolactasia", "milk sugar intolerance", "lactose malabsorption", "dairy product intolerance", "cow milk intolerance", "lactase persistence", and "lactase non-persistence". The terms were combined with: "prevalence", "consequence", "implication", "epidemiology", "incidence", "polymorphism", "lct gene", "13910", "22018", "13915", "14010", "13907", "13914", "14009", "hydrogen breath test", "breath hydrogen test", "HBT", and "lactose tolerance test". No search limits were applied. Further details of the literature search are provided in the appendix (p 50). The references were imported into EndNote X7.

See Online for appendix

For the **protocol** see https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064802

Most included studies primarily assessed prevalence of lactose malabsorption or lactase persistence in specific areas; however, several studies had other primary aims (eg, assessing osteoporosis) but presented lactose malabsorption or lactase persistence as secondary results. Studies with no prevalence data, no data on number of participants, insufficiently described methodology, or populations with probable bias that were not representative of a general population were excluded.

We included studies presenting prevalence data of lactose malabsorption or lactase persistence among adults and children aged 10 years or older, and excluded studies in children aged younger than 10 years. Studies using self-reported data were excluded to limit information bias. Similarly, studies including inpatients and outpatients at gastroenterological wards were also excluded to avoid selection bias.

A range of methods for determining lactose malabsorption or lactase persistence were used, including genotyping, hydrogen breath tests, lactose tolerance tests, and urinary galactose excretion. For genotyping, the following SNPs were included: LCT 13907, 13910, 13914, 13915, 14009, 14010, and 22018. Various definitions were used for lactose malabsorption assessed by hydrogen breath tests including the following: a hydrogen concentration in expired breath of more than 20 ppm over baseline after ingestion of 50 g lactose; a hydrogen concentration in expired breath of more than 20 ppm over baseline after ingestion of 25 g lactose; a hydrogen concentration in expired breath of 10 ppm or more over baseline for at least two consecutive 15 min readings after ingestion of 50 g lactose; or a hydrogen concentration in expired breath of 30 ppm or more and a blood glucose increase of 1 mmol/L or more after ingestion of 50 g lactose. Similarly, lactose malabsorption assessed by lactose tolerance tests had a range of definitions including the following: a peak blood glucose increase of 20 mg/dL or lower in the capillary blood above fasting levels (or rise of 21–25 g/100 mL together with symptoms of intolerance) within 24 h after ingestion of lactose; a blood glucose increase of less than 20 mg/dL over the fasting level at any timepoint after ingestion of lactose; a galactose to creatinine ratio of less than 0·075 (mg/mg) in pooled 2 h urine samples following ingestion of 40 g lactose; a lactase activity of below 25 units/g of protein; a blood glucose increase of 20 mg/100 mL or less after ingestion of 1 g lactose per kg bodyweight; a blood glucose increase of 26 mg/dL or less after ingestion of 1 g of lactose per kg bodyweight; or a capillary glucose level increase of less than 1·1 mmol/L, immediately and 40 minutes after ingestion of 50 g lactose in 400 mL water after overnight fasting.

The imported references were screened by two authors (CLS and SKF) independently. Screening was done by reading the title and abstract, and assessing full-text articles deemed relevant. Data values were extracted by two authors (CLS and SKF) independently. All obtainable relevant papers were read in full text by two authors (CLS and SKF), and possible differences in assessment were discussed between all authors and resolved by consensus.

The protocol is registered with PROSPERO, number CRD42017064802, and is available online.

Data analysis

Data considered relevant were extracted into a Microsoft Excel table and information was gathered on sample size, method, lactose malabsorption prevalence or related measure (lactose malabsorbtion, lactase non-persistence, lactase persistence, lactase deficiency, lactase insufficiency, or adult type hypolactasia), year of publication, first author of article, study population characteristics including country, ethnicity, age, and sex, when described (appendix pp 58–78). For duplicate data identified, we used the data from the source published most recently. Supplementary files for included study populations or country measurements were assessed when available and regarded as relevant. For papers reporting on lactase persistence, data were converted to identify lactose malabsorption (one minus the frequency of lactase persistence).

For countries with more than one measure of lactose malabsorption, a combined measure was calculated using the weighted arithmetic mean. Analyses were done for all studies combined, primary sources only, genotyping studies only, hydrogen breath test studies only, and lactose tolerance test studies only. Standard errors for the confidence intervals in the prevalence measures were calculated with the formula (where $\dot{\rho}$ is the prevalence estimate and n is the number of participants in the studies):

$$\sqrt{(\dot{\rho} \times \frac{1-\dot{\rho}}{n})}$$

For global prevalence measures, estimates from each country were weighted according to the population size of the respective countries. In the global estimates, the standard error estimates used n for the number of studies included. The prevalence estimates are summarised in forest plots presented with 95% CIs for national and global estimates. R version 3.3.1 and Stata SE 11 were used for data analysis and graphical presentation. The R package rworldmap was used for graphical geographical presentation.

The risk of bias was assessed based on differences in accuracy of the various methods used. The included studies also used various definitions of lactose malabsorption, reflecting both incomplete consensus on the advantages and disadvantages of different diagnostic techniques and methodological development over time. Risk of bias was assessed using a tool developed by Hoy and colleagues.[17] Definitions, quality assessment score, and risk of bias of the included studies are shown in the

appendix (pp 32–49). A score of ten suggests low risk of bias, with increasing risk of bias as scores decrease. Studies with a score of less than nine points were excluded in sensitivity analyses. Heterogeneity between studies was evaluated using Q and I^2 statistics.[18] To explore potential heterogeneity, we did subgroup analyses by study characteristics. Small-study effects and publication bias were assessed using Egger's test and by inspection of the funnel plots.[19,20] For these plots, odds ratios were calculated as (study population LM_{sp}/non-LM_{sp})/(country estimates of LM_c/non-LM_c), where LM_{sp} is the proportion of lactose malabsorption in the study population, non-LM_{sp} is one minus the proportion of lactose malabsorption in the study population, similarly the LM_c is the proportion of lactose malabsorption in the country and non-LM_c is one minus the proportion of lactose malabsorption in the country. When Egger's test or funnel plots indicated bias, we tested whether this affected the results by excluding obvious outlying studies based on inspection of the funnel plots.

Role of the funding source

There was no funding for this study. CLS, SKF, and LTF had access to all the data in the study. LTF took responsibility for the decision to submit for publication.

Results

2655 records were identified in the search, and 10 additional records were identified through searching the reference lists of relevant reviews and full-text articles obtained. After exclusion of 500 duplicates, 1767 studies that were not relevant, 99 articles that were not accessible or did not meet language restrictions, 38 studies assessing only children younger than 10 years, and 140 for other reasons, 116 full-text articles were included, contributing 306 different study populations (figure 1). 47 papers presented data with genotyping, 41 used hydrogen breath tests, 24 used lactose tolerance tests, two used urinary galactose excretion, one used biopsy, and one used both genotyping and lactose tolerance tests (appendix pp 52–57). From secondary sources, 59 of 82 articles assessed were added (23 were excluded due to no information on study size; figure 1). This provided an additional 144 study populations (appendix pp 73–78). Of the study populations from both primary and secondary sources (n=450), 231 used genotyping, 83 used hydrogen breath tests, 101 used lactose tolerance tests, and 35 used other methods or did not describe the methods sufficiently (appendix p 30). The studies included 62 910 participants, of whom 50 030 were from primary sources and 12 880 from secondary sources. The included studies are described in further detail in the appendix (pp 53–157), and references for both screened and included studies are provided.

The studies included data from 89 countries, which covers 84% of the world's population. When standardising for country size, the global prevalence of lactose malabsorption was 68% (95% CI 64–72; appendix pp 8–12). When excluding secondary sources, the estimate was 67% (61–72) based on data from 81 countries, covering about 81% of the world's population. The frequency varied widely between countries (figure 2). The regional prevalence was 64% (54–74) in Asia (except Middle East), 47% (33–61) in eastern Europe, Russia, and former Soviet Republics, 38% (CI 18–57) in Latin America, 70% (57–83) in the Middle East, 66% (45–88) in northern Africa, 42% (13–71) in northern America, 45% (19–71) in Oceania, 63% (54–72) in sub-Saharan Africa, and 28% (19–37) in northern, southern and western Europe. Lactose malabsorption is widespread in most of Asia, ranging from 58% in Pakistan to 100% in South Korea (figure 3). In the Middle East, the situation was similar except for lower estimates in Cyprus (16%) and Saudi Arabia (28%; figure 3). Some regions including western and northern Europe had a low-to-moderate prevalence (4–36%; figure 3). In eastern Europe, lactose malabsoprtion was moderate-to-high (28–81%; figure 3). Lactose malabsorption was also widespread in Africa

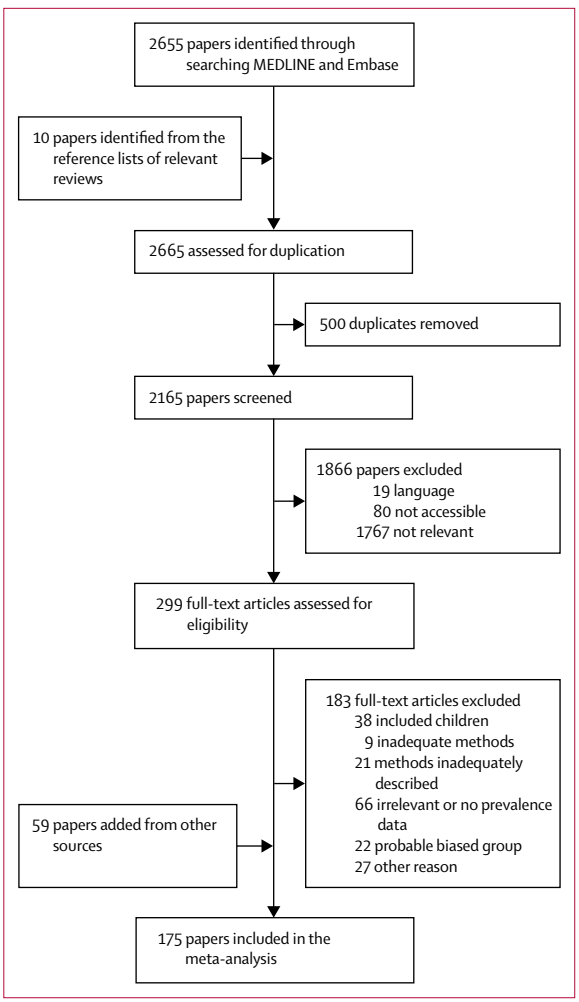

Figure 1: **Study selection**

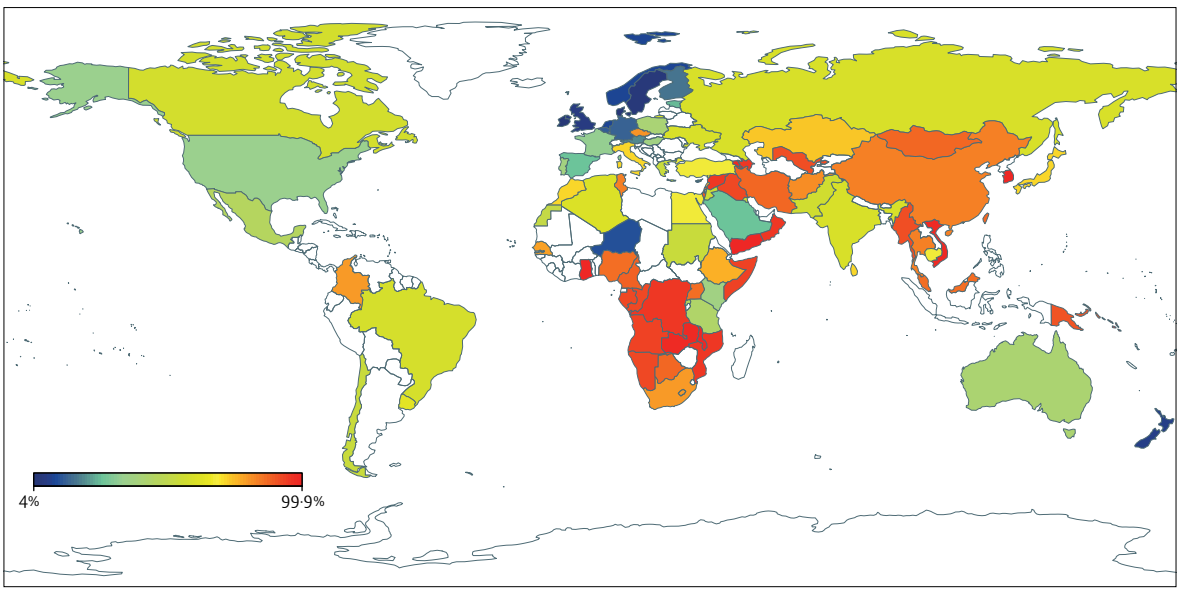

Figure 2: **Prevalence of lactose malabsorption in different countries assessed with all methods**

including northern Africa (53–84%) and sub-Saharan Africa (77–100%), with the exception of Niger (13%), Kenya (39%), Sudan (55%), and Tanzania (45%). In the Americas, the prevalence estimates ranged from 36% in the USA to 80% in Colombia (figure 3). The frequency in various countries stratified by testing methods is presented in further detail in the appendix (pp 8–11).

Genotyping studies generally indicated higher lactose malabsorption estimates than did hydrogen breath test and lactose tolerance test studies. Using only genotyping data, the estimated global prevalence of lactose malabsorption was 74% (95% CI 69–80; from 67 countries). Using only lactose tolerance test data gave an estimate of 55% (46–65, from 45 countries), and using hydrogen breath test data 57% (46–67, from 38 countries; appendix pp 9–11).

There was substantial heterogeneity between studies within most of the assessed countries (appendix pp 13–20). Egger's test and inspection of funnel plots indicated some small-study effects or publication bias for some countries including Ethiopia, Russia, and China (appendix pp 21–29). Inspection of scatter plots also indicated some study population outliers.

Of the included articles, 13 had random selection, but most studies ranked acceptable in the other evaluated criteria (appendix pp 32–49). The quality scoring of the primary articles indicated that 12 articles had a score of ten, 76 had a score of nine, 26 a score of eight, and two articles a score of seven. In sensitivity analyses excluding study populations from articles with a score of less than eight points, the global prevalence was 69% (95% CI 65–73), and excluding those with a score of eight points or less, the prevalence was 68% (64–73). Exclusion of studies based on outliers from funnel plots gave a prevalence of 61% (56–66), whereas excluding both outliers and articles with a score of eight or less gave a prevalence of 62% (57–67).

Discussion

Our findings show that lactose malabsorption is widespread in most of the world, with wide variation between countries and regions and, to some degree, also within countries. The overall estimated frequency of lactose malabsorption in this study is around two-thirds of the world's population. Some countries such as Canada and Australia had large internal variation in lactose malabsorption between native populations and other groups. This is probably linked to the preferential development of lactase persistence during the last 5000–10 000 years, particularly in areas where domesticated cattle have been important historically.[21] This was particularly the case in northern Europe and some other regions (including several nomadic tribes), where dairy products became a key component of the diet, thus contributing to an evolutionary pressure to develop the ability to digest lactose. In these regions, SNPs linked with lactase persistence are common. However, large migrations have contributed to the coexistence of groups of people with different tolerance for lactose in the same areas, such as for people with European ancestors migrating to the Americas and Australia.[21]

Since there is no complete agreement on a gold standard for measuring and defining lactose malabsorption,[7,22–26] assessing sensitivity and specificity of the different testing methods is challenging. Initially, sampling of jejunal biopsies was suggested as a gold standard,[27,28] but this method has been criticised as unreliable because of the irregular distribution of lactase activity in the small intestinal mucosa.[24] Jejunal biopsies have, to some extent, been replaced by endoscopic duodenal biopsy, mainly because of the invasiveness of jejunal biopsies.[29] In clinical practice, biopsies are often too expensive and invasive, and hydrogen breath testing

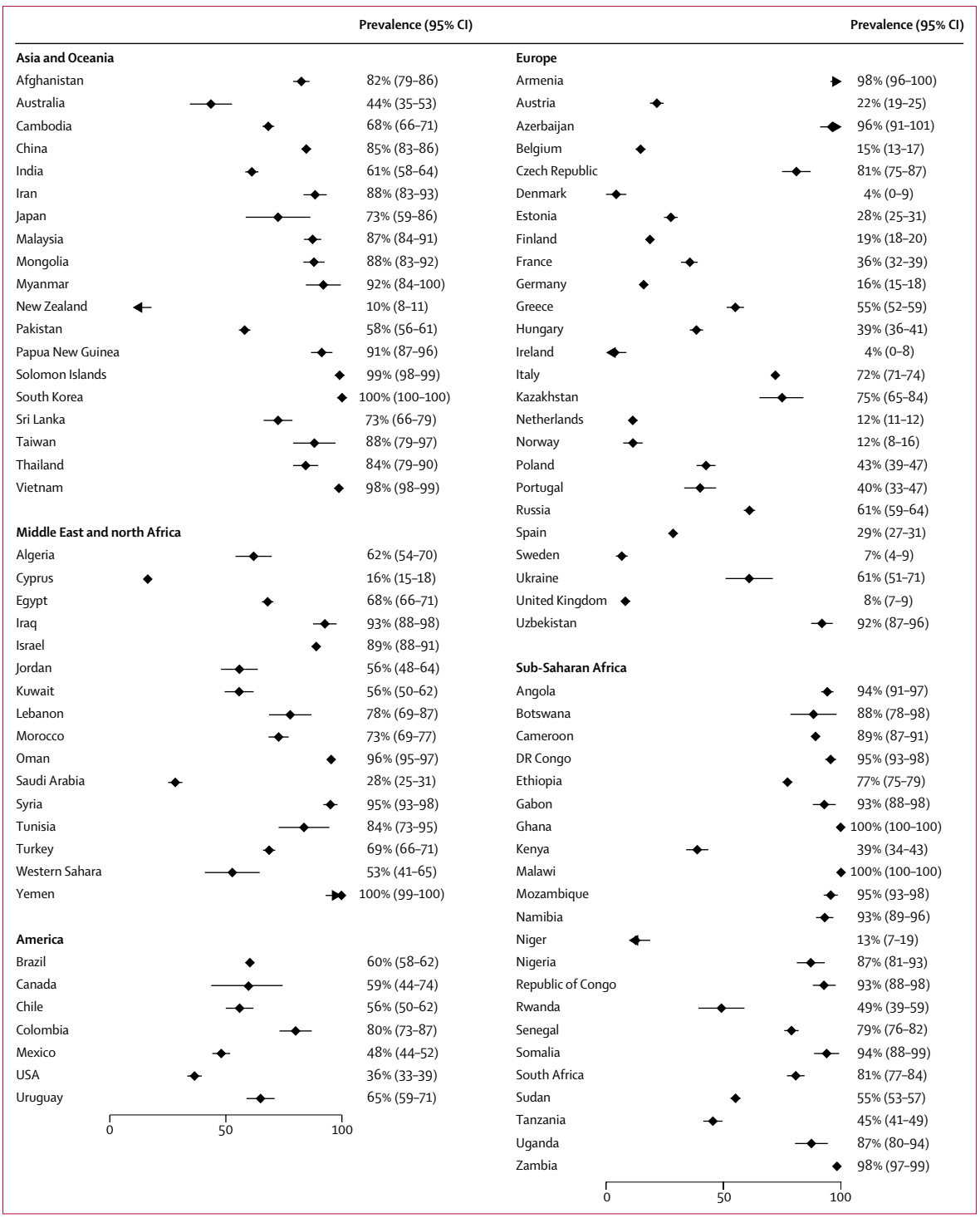

Figure 3: **Regional lactose malabsorption prevalence and country estimates in Asia and Oceania, the Middle East and northern Africa, America, Europe, and sub-Saharan Africa**

has therefore most commonly been used.[30] One of the first studies examining the sensitivity and specificity of hydrogen breath tests showed that, when using 50 g of lactose, sensitivity and specificity were both 100% compared with lactase activity measured by mucosal biopsy.[28] However, a more recent systematic review showed a sensitivity for both hydrogen breath tests and lactose tolerance tests of 78% and a specificity of 93%

(using 25 g lactose with 16 ppm and 0·9 mmol/L as cutoffs, respectively).[24] For lactose tolerance tests, the sensitivity has been estimated to be 76–94%, and specificity 77–96%.[31] Most of the included studies used test doses of 50 g and few studies used test doses of 25 g or less. Thus, further comparisons between high and low doses could not be made.

A recent meta-analysis compared hydrogen breath tests and lactose tolerance tests with genotyping of the north-European-associated polymorphism C/T-13910.[32] For lactose tolerance tests, the sensitivity was 94% (95% CI 90–97) and specificity 90% (84–95), whereas for hydrogen breath tests the overall sensitivity was 88% (85–90) and specificity 85% (82–87). Increased dosage (50 g *vs* 25 g) resulted in higher sensitivity (92% *vs* 82%) at the expense of lowered specificity (83% *vs* 95%). When comparing hydrogen breath tests and lactose tolerance tests with genotyping in areas where the C/T-13910 variant is not the dominant lactase persistence polymorphism, discrepancies are seen for studies not including all relevant lactase persistence polymorphisms.[15,33–36] This is especially prominent in sub-Saharan Africa, the Middle East, and northern China, in which genotyping results based only on C/T-13910 suggest an inaccurately low frequency of lactase malabsorption. Genotyping has been criticised for this reason and also because it does not capture information on clinical manifestations or symptoms.[37] Furthermore, genotyping does not detect secondary lactose malabsorption—eg, due to gastroenteritis, visceral surgery, and other diseases.[8] Since estimation of the prevalence of lactose malabsorption using genotyping depends on inclusion of all relevant polymorphisms related to lactase persistence in the respective population, a need for further investigation in some areas has been suggested.[15]

It is also worth noting that different definitions and cutoff values for hydrogen breath tests and lactose tolerance tests have been used. Most hydrogen breath test studies used a cutoff of 20 ppm to diagnose lactose malabsorption. In one study, increasing the cutoff from 10 ppm to 15 ppm or 20 ppm resulted in 7–13% lower prevalence figures, but the different doses showed similar differences between healthy controls and groups of patients with various chronic intestinal disorders.[38]

Because lactase persistence decreases with age, age is of importance when assessing lactose malabsorption.[14] Studies of children indicate decreasing lactase activity with age, and lactose malabsorption is generally rare early in infancy, approaching adult levels around the age of 7–10 years.[9,39–42] The occurence of lactose malabsorption generally increases with age and seems to increase more sharply in populations where the prevalence of lactose malabsorption is high.[9] Thus, our findings are generalisable for children from the age of 10 years and to some degree also to slightly younger children in populations where the prevalence of lactose malabsorption is high.

The prevalence of lactose malabsorption in older adults is reported to be somewhat higher than in younger adults.[43,44] The cause of the discrepancy has been suggested to be related to small intestinal bacterial overgrowth in older adults rather than declining lactase activity.[45] The clinical implications of this observation have not been clearly investigated. We chose to include all studies that include adults and children aged 10 years or older because many studies do not clearly differentiate between younger and older adults and the cutoffs regarding older age varies.

In addition to lactose malabsorption, a wide range of related terms have been used in the literature. Lactase non-persistence, lactase deficiency, lactase insufficiency, and adult type hypolactasia describe a state of lower intestinal lactase concentrations relative to those in infants.[7] Lactose malabsorption nearly completely correlates with lactase non-persistence, but in principle more accurately reflects the ability to absorb an ingested amount of lactose.[8] Lactose intolerance describes symptoms associated with lactose malabsorption and is more difficult to measure objectively. The assessment of lactose intolerance is often done by registering symptoms during a lactose challenge, but few studies have done this using a blinded approach.[7,46] Interpretation of self-reported symptoms might be complicated by placebo responses,[46] and a discrepancy between perception of food intolerance and results of double-blind, placebo-controlled food challenges has been shown.[47] Self-reported milk intolerance has shown low sensitivity (30–71%) and specificity (25–87%), and prescription of a lactose-restricted diet to all patients with self-reported symptoms is therefore not recommended.[5] However, intolerance symptoms can be dose-related with a cumulative appearance, which might be difficult to replicate with blinded testing.

From a clinical perspective, substantial overlap between lactose intolerance and other gastroenterological diseases has been observed.[48] This especially applies for irritable bowel syndrome, which has a similar symptom profile to lactose intolerance, but also for inflammatory bowel disease.[48–51] For irritable bowel syndrome, lactose is often among the main stressors causing symptoms, with consequences for management, and dietary changes including limited lactose consumption have shown benefits in several studies.[51,52] However, blinded studies have shown that most patients with lactose malabsorption can tolerate 12–18 g of lactose before experiencing symptoms.[53] With intake of exogenous lactase, and to some degree probiotics, lactose is generally better tolerated.

Most cultures have traditional food patterns in line with food tolerance patterns.[54] However, keeping lactose malabsorption patterns in mind when providing food aid, for example during famine outbreaks, is of importance to limit bothersome symptoms, particularly for adults and adolescents. For clinicians, recognition of

lactose malabsorption patterns could also help to identify likely causes for related symptoms and guide optimal management.

This study has several strengths and some limitations. Although several reviews have been published, few systematic reviews and no meta-analyses have been published, and to our knowledge, ours is the only systematic review and meta-analysis to include studies published after 2009.[7,9,14,15] We have presented detailed data on national levels, as well as regional and global estimates. Some data might have been missed due to inadequate indexing in MEDLINE and Embase (particularly for older studies), or titles and abstract not indicating the articles to be of relevance. Additionally, we could not acquire several articles, mostly because electronic versions were not available and paper versions could not be obtained; however, for several of these we managed to gather data through secondary sources. It is possible that we have missed some relevant data or misinterpreted insufficiently described data. Inadequately described study methods (eg, lacking specification of ethnicity, sample size, and description of study population) might have resulted in rejection of otherwise relevant studies. For many countries, there is substantial within-country heterogeneity, which could be explained partly by differences in lactose malabsorption between different ethnicities within the same country and migration.[21] Thus, accurate national estimates are strongly dependent on an appropriate representation of the ethnicities of a country's population. In some countries, such as Russia, Canada, and Australia, the included populations might not have been representative of the overall population, because minority populations seemed to be over-represented. For these countries, this is likely to have resulted in overestimation of the prevalence of lactose malabsorption. For most countries, the weighting used to account for differences in study size have probably limited such effects.

In conclusion, lactose malabsorption is widespread in most of the world, with wide variation between different regions and an overall frequency of around two-thirds of the world's population.

Contributors

All authors conceived and designed the study, acquired, analysed, and interpreted the data, checked data extraction, and drafted the manuscript. All authors were involved in defining the search criteria, CLS and SKF screened the included references, all authors discussed cases with uncertainty relating to inclusion and categorisation, and LTF coordinated statistical analysis and graphical presentation. All authors wrote the manuscript in collaboration, have read and approved the final manuscript, have had full access to the data, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

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