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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested by the Office of Medical Applications of Research (OMAR) at the National Institutes of Health (NIH). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Objectives: We systematically reviewed evidence to determine lactose intolerance (LI) prevalence, bone health after dairy-exclusion diets, tolerable dose of lactose in subjects with diagnosed LI, and management.

Data Sources: We searched multiple electronic databases for original studies published in English from 1967-November 2009.

Review Methods: We extracted patient and study characteristics using author's definitions of LI and lactose malabsorption. We compared outcomes in relation to diagnostic tests, including lactose challenge, intestinal biopsies of lactase enzyme levels, genetic tests, and symptoms. Fractures, bone mineral content (BMC) and bone mineral density (BMD) were compared in categories of lactose intake. Reported symptoms, lactose dose and formulation, timing of lactose ingestion, and co-ingested food were analyzed in association with tolerability of lactose. Symptoms were compared after administration of probiotics, enzyme replacements, lactose-reduced milk and increasing lactose load.

Results: Prevalence was reported in 54 primarily nonpopulation based studies (15 from the United States). Studies did not directly assess LI and subjects were highly selected. LI magnitude was very low in children and remained low into adulthood among individuals of Northern European descent. For African American, Hispanic, Asian, and American Indian populations LI rates may be 50 percent higher in late childhood and adulthood. Small doses of lactose were well tolerated in most populations. Low level evidence from 55 observational studies of 223,336 subjects indicated that low milk consumers may have increased fracture risk. Strength and significance varied depended on exposure definitions. Low level evidence from randomized controlled trials (RCTs) of children (seven RCTs) and adult women (two RCTs) with low lactose intake indicated that dairy interventions may improve BMC in select populations. Most individuals with LI can tolerate up to 12 grams of lactose, though symptoms became more prominent at doses above 12 grams and appreciable after 24 grams of lactose; 50 grams induced symptoms in the vast majority. A daily divided dose of 24 grams was generally tolerated. We found insufficient evidence that use of lactose reduced solution/milk, with lactose content of 0-2 grams, compared to a lactose dose of greater than 12 grams, reduced symptoms of lactose intolerance. Evidence was insufficient for probiotics (eight RCTs), colonic adaptation (two RCTs) or varying lactose doses (three RCTs) or other agents (one RCT). Inclusion criteria, interventions, and outcomes were variable. Yogurt and probiotic types studied were variable and results either showed no difference in symptom scores or small differences in symptoms that may be of low clinical relevance.

Conclusions: There are race and age differences in LI prevalence. Evidence is insufficient to accurately assess U.S. population prevalence of LI. Children with low lactose intake may have beneficial bone outcomes from dairy interventions. There was evidence that most individuals with presumed LI or LM can tolerate 12-15 grams of lactose (approximately 1 cup of milk). There was insufficient evidence regarding effectiveness for all evaluated agents. Additional research is needed to determine LI treatment effectiveness.

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Executive Summary

Introduction

Milk and milk products contain high concentrations of the disaccharide lactose (galactose and glucose linked by a beta-galactoside bond). Intestinal absorption of lactose requires that the disaccharide be hydrolyzed to its component monosaccharides, both of which are rapidly transported across the small bowel mucosa. A brush border beta-galactosidase, lactase, carries out this hydrolysis. While infants virtually always have high concentrations of lactase, sometime after weaning a genetically programmed reduction in lactase synthesis results in very low lactase activity in some adult subjects, a situation known as lactase nonpersistence.

Lactase nonpersistence results in incomplete digestion of an ingested load of lactose; hence lactose is malabsorbed and reaches the colon. If sufficient lactose enters the colon, the subject may experience symptoms of abdominal pain, bloating, excess flatulence, and diarrhea, a condition known as lactose intolerance (LI). Diseases of the small bowel mucosa (infection, celiac disease) may also be associated with low brush border lactase, with resultant lactose malabsorption (LM) and LI.

The terminology involved in lactose absorption/intolerance is as follows:

a) Lactase nonpersistence (or lactase insufficiency) – indicates that brush border lactase activity is only a small fraction of the infantile level, a condition documented by analysis of brush border biopsies. Recently it has been shown that a genotype (C/C) of the lactase promoter gene is responsible for lactase nonpersistence, and demonstration of this genotype can be used as indirect evidence of lactase nonpersistence.
b) Lactose malabsorption – indicates that a sizable fraction of a dosage of lactose is not absorbed in the small bowel and thus is delivered to the colon. Since such malabsorption is virtually always a result of low levels of lactase, there is a nearly a one to one relationship of lactase nonpersistence (or deficiency) and LM. LM is objectively demonstrated via measurements of hydrogen H_2 breath or blood glucose concentrations following ingestion of a lactose load.
c) Lactose intolerance – indicates that malabsorbed lactose produces symptoms (diarrhea, abdominal discomfort, flatulence, or bloating). It should be stressed that this symptomatic response to LM is linked to the quantity of lactose malabsorbed (as well as other variables), i.e., ingestion of limited quantities of lactose does not cause recognizable symptoms in lactose malabsorbers, while very large doses commonly induce appreciable LI symptoms. As a result, the prevalence of lactase nonpersistence or LM could far exceed the prevalence of LI symptoms in population groups ingesting modest quantities of lactose.

A public health problem may arise when large numbers of individuals diagnose themselves as being lactose intolerant. However, these self-identified lactose intolerant individuals may actually be lactase persisters. Some of these lactase persisters (and even lactase nonpersisters) may mistakenly ascribe the symptoms of undiagnosed irritable bowel syndrome (IBS) or other intestinal disorders to LI. Given that the relatively nonspecific abdominal symptoms caused by IBS and LM are extremely susceptible to the placebo effect, reliable demonstration of LI requires double-blind methodology.

The problem may become intergenerational when self-diagnosed lactose intolerant parents place their children on lactose restricted diets (even in the absence of symptoms) or use enzymatic replacement in the belief that the condition is hereditary. Children and adults with LI may avoid dietary milk intake to reduce symptoms of intolerance. Since the avoidance of milk and milk containing products can result in a dietary calcium intake that is below recommended levels of 1,000 milligrams (mg) per day for men and women and 1,300 mg for adolescents, osteoporosis and associated fractures secondary to inadequate dietary calcium is the perceived major potential health problem associated with real or assumed LI.

Current dietary recommendations suggest consuming 3 cups/day of fat-free or low-fat milk or equivalent milk products. This amount is equivalent to about 50 grams of lactose, which we defined to be the threshold of minimum tolerance. We defined LI to be present when ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject induces gastrointestinal symptoms not observed when the subject ingests an indistinguishable placebo.

Because ingesting smaller portions over the course of the day may minimize potential problems with larger acute lactose loads, the above definition of lactose intolerance may miss lactose malabsorbers who ingest smaller dosages of lactose. The prevalence of clinically important lactose intolerance requires demonstration that the quantity of lactose that subjects actually ingest (or wish to ingest) causes symptoms in placebo-controlled experiments.

Treatment to reduce lactose exposure, while maintaining calcium intake from dairy products, consists of a lactose restricted diet or the use of milk in which the lactose has been pre-hydrolyzed via treatment with lactase supplements. Lactase supplements taken at the time of milk ingestion also are commercially available.

This report was commissioned as background material for a National Institutes of Health (NIH) and Office of Medical Applications of Research (OMAR) Consensus Development Conference on Lactose Intolerance and Health to address the following key questions:

Key Questions Addressed in this Report

1. What is the prevalence of lactose intolerance? How does this differ by race, ethnicity, and age?
2. What are the health outcomes of dairy exclusion diets?
    - In true lactase nonpersisters
    - In undiagnosed or self-identified lactose intolerant individuals.
    - How does this differ by age and ethnicity?
    - Health outcomes to include: Bone health – osteoporosis, fracture, bone density, bone mass; and gastrointestinal symptoms – abdominal pain, diarrhea, nausea, flatulence, bloating.
3. What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?
    - How does this differ by age and ethnicity?
    - What are the diagnostic standards used?
4. What strategies are effective in managing individuals with diagnosed lactose intolerance?
    - Commercially-available lactase
    - Prebiotics and probiotics
    - Incremental lactose loads for colonic adaptation
    - Other dietary strategies
5. What are the future research needs for understanding and managing lactose intolerance?

Methods

We searched several databases including MEDLINE® via PubMed® and via Ovid, the Cochrane Library of randomized controlled clinical trials, BIOSIS Previews®, Biological Abstracts®, Global Health, Food Science and Technology Abstracts®, and Commonwealth Agricultural Bureau International databases, to find studies published in English between 1967 and November 2009. We included observations that examined prevalence, symptoms, and outcomes of LI in different age, gender, racial, and ethnic groups. We excluded populations with other gastrointestinal disorders, including individuals diagnosed with IBS, inflammatory or infectious bowel diseases, or milk allergies. We excluded children younger than 4 years of age.

We synthesized the results using the exact definitions the authors used for LI and LM. We defined LI to be present when ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject induces gastrointestinal symptoms not observed when the subject ingests an indistinguishable placebo. Since the symptomatic response to lactose likely increases with increasing dosages, this definition is also intimately related to the dose of lactose administered.

For question 2 we operationalized dairy exclusion diets by including studies that compared outcomes among populations reporting, or randomized, to consume diets very low in or free from lactose. We included the following populations: general, vegans, lactase nonpersisters, diagnosed or self-identified lactose intolerant or lactose malabsorber. For bone health outcomes we analyzed bone fractures and osteoporosis, bone mineral content (BMC), and bone mineral density (BMD). For gastrointestinal outcomes we assessed gastrointestinal symptoms at different categories of lactose intake. Dietary recall may be unreliable, and our search identified few studies meeting these criteria. Therefore, we included studies that examined the association between individuals classified as lactose intolerant, lactose malabsorbers, or lactase deficient and health outcomes even if they did not specifically state the amount of lactose/dairy consumed. We included these studies because evidence suggested that these populations were likely to consume diets low in lactose. We provide quantitative estimation of lactose intake expressed in differences between consumed and recommended dietary calcium. We included randomized controlled trials (RCTs) that evaluated the effect of lactose free diets on outcomes to assess if lactose intake resulted in improved bone health. We excluded the studies of patients with milk allergies, irritable bowel syndrome, chronic diarrhea, gastroenteritis, or other diagnosed gastrointestinal diseases.

Osteoporosis was defined according to World Health Organization criteria[1-3] as a BMD 2.5 standard deviation or more below the young average value in women and men.[4] Osteopenia was defined as a BMD 1-2.5 standard deviation below the population average.[5]

We used reference data on femur bone mineral content and density of noninstitutionalized adults in the United States from the third National Health and Nutrition Examination Survey that collected dual energy x-ray absorptiometry in a nationally representative sample of 14,646 men and women 20 years of age and older.[6]

For Key Question 3 we included double-blind RCTs and analyzed the tolerable dose of lactose given in single or multiple doses. Findings from these studies (and for question 4) provided information regarding the short-term gastrointestinal outcomes among subjects diagnosed with LI or LM.

For Key Question 4 we included randomized double blind controlled trials of probiotics, enzyme replacement therapies with lactase from nonhuman sources, administration of lactose

reduced milk, and regimes of increases in dietary lactose load. We evaluated the efficacy of therapeutic agents and strategies in alleviating symptoms among individuals with diagnosed lactose malabsorption.

We judged level of evidence using modified GRADE criteria. Inconsistency in direction or magnitude of the association or inconsistent adjustment for known confounding factors reduced level of evidence. We also determined low level of evidence and confidence when data came from a single study. We judged moderate level of evidence for statistically heterogeneous results from several small RCTs because further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Results

Key Question 1: What is the prevalence of lactose intolerance? How does this differ by race, ethnicity, and age?

A total of 54 articles met inclusion criteria, including 15 articles from the United States. Studies did not directly assess LI in a blinded lactose challenge but instead assessed unblinded subjective LI symptoms, an inability to fully absorb lactose (lactose malabsorption), or lactase nonpersistence. The data available tended to be from highly selected populations and was not likely representative of the overall U.S. population. We report results according to the following conditions: lactose intolerance, lactose malabsorption, or lactase nonpersistence. Within these conditions we further describe findings according to assessment method and populations studied.

Lactose intolerance.

Symptoms following blinded lactose challenge. We identified no studies that reported on the prevalence of LI based on our "gold-standard" definition; i.e., gastrointestinal symptoms that are more prevalent and severe after ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject that are not observed when the subject ingests an indistinguishable placebo.

Symptoms following nonblinded lactose challenge. We identified 21 studies that reported LI-related symptoms (abdominal pain, bloating, excess flatulence, and diarrhea) following a nonblinded lactose challenge.[7-28] Few assessed U.S. populations. No studies were published in the last 30 years. There were four older U.S. convenience sample studies[13,18,26,27] that reported results on different subpopulations. One study of healthy Caucasian volunteers with no history of milk intolerance reported that symptoms were rare and confined primarily to those with biopsy determined hypolactasia.[18] In another study on healthy adults,[26] Hispanics were 43 percent more likely to report symptoms following a lactose challenge compared to white non-Hispanics.[26] Similarly, in healthy children[27] the rate of symptoms was twice as high among Hispanic children (41 percent versus 20 percent in non-Hispanic). The fourth U.S. study included African American (n=69) and Caucasian (n=30) children between the ages of 4 and 9 years old. The overall frequency of symptoms following a challenge was quite low in young children, but the rate increased with age and was higher in African American children compared to Caucasian children.[13] Age up to adulthood was a consistent predictor of LI-related symptoms. Racial and ethnic variation was present, but the variation in symptoms reported following a challenge did not seem as extreme as the racial and ethnic variation seen in lactose malabsorption and prevalence of lactase nonpersistence.

Symptoms without lactose challenge. We identified seven studies reporting baseline self-reported symptoms in 6,161 people.[29-35] There was only one U.S. population-based study.[35] This study included only self-reported LI with no additional confirmation of the diagnosis. Overall, U.S. estimated prevalence of self-reported LI was 12 percent from this study, with estimates of 8 percent in European Americans, 10 percent in Hispanic Americans, and 20 percent in African Americans. The rest of the self-reported studies' results provide little evidence to address our research questions about population prevalence and the impact of age and ethnicity. Overall, the prevalence of self-reported symptoms was typically lower than the prevalence of symptoms following a lactose challenge.

Lactose malabsorption.

Determined by hydrogen breath test following lactose challenge. We identified 31 studies evaluating participants from a wide range of ages and ethnicities that reported LM prevalence as defined by subjects with a positive hydrogen breath test.[7,8,11,12,14-17,20-25,28,30,32,36-48] None of the U.S. studies were representative population-based studies. All U.S. studies focused on reporting results in populations of patients with gastrointestinal (GI) symptoms at baseline,[36,42,47,48] with the exception of one three decade old study of American Indians[30] and one convenience sample of adults from the Army, senior centers, nursing homes, and a university.[44]

Within the U.S. studies of patients with GI symptoms at baseline, the prevalence of LM in Caucasian adult populations ranged from 6 to 24 percent.[42,44,47] Some data suggested high levels of LM among American Indians, but this effect was substantially attenuated among those with American Indian and Caucasian mixed ancestry.[30] One study showed that the prevalence of LM may be greater than 70 percent in African Americans, around 50 percent in Hispanic Americans, and even higher for Asian Americans.[49] Age is an important contributor to the rate of LM, since nearly every population group identified showed low rates of LM in the youngest age groups, particularly those less than 6 years of age.[16,17,23,28,39,45,46] In populations with high adult rates of LM, rates peaked between 10 and 16 years of age.

Lactase nonpersisters (adult-type hypolactasia).

Biopsy identification. We identified five studies that reported on the prevalence of lactase persistence as diagnosed by biopsy assays.[18,50-53] These estimates ranged from 6 percent to 34 percent among Caucasians, to 75 percent among nonwhites; however, there was little to no correlation with symptoms of LI. It is difficult to generalize these findings to create population estimates or understand their clinical relevance.

Genetic Test Association. The most commonly reported genetic mutation for adult-type hypolactasia is the single nucleotide polymorphism (SNP) of the lactase (LCT) gene. The C allele is the globally most prevalent allele, while the less common T allele is dominantly associated with lactase persistence.[54] Nine studies were identified that reported genotype frequencies for LCT -13910C>T SNP mutation, indicating a genetic predisposition for hypolactasia, or lactose nonpersistence.[29,45,55-61] None of these studies were of U.S. populations. There were no obvious differences in genotype by age group.[55,56] In North European studies, Caucasians had frequencies between 10-20 percent for the homozygous C/C genotype.[29,55-57,59,61]

Key Question 2: What are the health outcomes of dairy exclusion diets?

We identified 55 publications of observational studies of 223,336 subjects that reported symptoms or bone health outcomes in relation to lactose intake. The absence of specific

documentation of the amount of lactose consumed over long periods of time hampered synthesis, so indirect associations between bone outcomes and proxy variables for lower lactose consumption were assessed. We also found seven RCTs of 1,207 children on low lactose diets (less than 50 percent of the recommended calcium intake), and two RCTs of adult women (34-73 percent of recommended calcium intake) [62,63] that provide direct evidence of lactose intake on bone health. African American women were enrolled in one study.[64] We identified no studies that specifically addressed gastrointestinal symptoms after long-term (>1 month) dairy exclusion diets. In evidence presented for key questions 3 and 4 we report on short-term gastrointestinal symptoms after blinded administration of lactose free diets or differing doses of lactose intake among subjects diagnosed with LI or LM. We included indirect evidence of the effect of dairy exclusion diets on health outcomes in populations that are presumed to have low dairy intake (e.g., vegans, individuals with LI/LM or lactase nonpersistence), even if the studies did not report on the amount of dairy consumed.

Lactose and calcium. Children and adults with self-reported symptoms of milk intolerance and diagnosed LM reported (or were assumed to be consuming) lactose free or low lactose diets. Limited evidence suggest that adults with C/C genotype may report reduced milk intake.[59,65-67] The association was more consistent for women.[68,69] Young adults with C/C genotype reported not drinking milk two times more often than those with TT genotype.[70] The association may diminish with aging.[71,72]

Dietary calcium intake was 47 percent of that recommended in children and 30 percent in women who followed a vegan diet. Among those with LI, children consumed 45 percent and women 37 percent of the recommended dietary calcium. During the transition to young adulthood, adolescents with LI had decreased dairy calcium intake.[73] Among those with LM, adults consume 44 percent and women 50 percent of the recommended dietary calcium. Daily calcium intake was 32 percent of that recommended in women with LM and LI. Young adults with C/C genotype had lower than recommended calcium intake when compared to those with TT genotype.[70] Women with C/C genetic polymorphism consumed 48 percent of the recommended dairy calcium from all sources and 34 percent from milk. Men with C/C genetic polymorphism consumed 58 percent of the recommended dairy calcium from all sources and 1.3 percent from milk. Children with C/C genetic polymorphism consumed 80 percent of the recommended dietary calcium.

We evaluated GI symptoms and bone health in vegans (lactose free), in healthy adults with low lactose intake and an unknown proportion of subjects with undiagnosed LI, and in populations with lactase deficiency, LI, or LM who followed low lactose diet.

Association between GI symptoms and dairy exclusion diets. We identified no studies that addressed the long-term impact (>1 month) of dairy exclusion diets on GI symptoms in the general population, vegans, or those diagnosed with LI or LM. Limited evidence suggested that long-term lactose free diet resulted in improved symptoms in patients with IBS and lactose malabsorption.[74] A degree of clinical improvement, however, was not associated with severity of clinical symptoms during hydrogen diagnostic tests in patients with IBS and no history of milk intolerance.[75] Therefore, severity of clinical symptoms during hydrogen diagnostic tests could not predict favorable responses to long-term lactose free diets. Postmenopausal Austrian women with TT genotype (lactase persistence) had lower odds of aversion to milk consumption than women with C/C genotype.[68,69] Among children who avoided milk, those diagnosed with lactose intolerance had much greater odds of milk related symptoms.[76]

In key questions 3 and 4 we report short-term GI outcomes from blinded RCTs among subjects with diagnosed LI or controls fed short-term diets containing varying doses of lactose or lactose free diets.

Association between lactose intake and metabolism and bone fractures. We found low levels of evidence from observational studies that low milk consumers had fractures more frequently than populations with higher milk consumption. Inconsistency in magnitude of the association and lack of consistent adjustment for all known confounding factors lowered the level of evidence.[76-88] The magnitude varied depending on definitions of exposure. Studies did not analyze all levels of exposure, including milk and dairy calcium intake, genetic polymorphism, perceived milk intolerance, and positive tests for lactose maldigestion. We found low levels of evidence from two industry sponsored studies that children who avoid milk intake for more than 4 months had increased risk of bone fractures.[76,89]

A single study found that odds of the annual incidence of distal forearm fracture in prepubertal children with a history of long-term milk avoidance more than doubled.[76] Another study reported that the age-adjusted odds of history of any fracture were more than three times higher among children with lactose free diets compared to the general population.[89] We found low levels of inconsistent evidence from three studies of 44,552 adults (not stratified by gender) that those with low lifetime or childhood milk intake had increased odds of any or osteoporotic fracture.[80] Evidence from nine studies of 111,485 adult women suggested an increase in risk of fracture in association with low dairy intake. The magnitude of the association varied across the studies. Variability in definitions of lactose intake and types of fracture may contribute to inconsistency in the results of the studies. While all nine studies found increased odds of fracture in women with lower dairy intake; only five reported a significant association.[77-79,81,82,84-87] We found no significant association between any osteoporotic or hip fracture and low milk intake among male participants in large well designed observational studies.[83,88] One large cohort reported that vegans had increased relative risk of fractures compared to the general population.[90]

Genetic predisposition. We found no studies that examined the association of low versus regular lactose diet and bone outcomes in those with genetic diagnosis, probably because of high prevalence of low lactose diet in this population However, we found studies that compared bone outcomes in subjects with C/C genotype (true lactase nonpersisters) and TT genotype (lactase persisters). The association between a single nucleotide polymorphism of the LCT gene at chromosome 2q21-22 (associated with lactase deficiency and reduced lactose intake) and fractures in adults was examined in five publications.[29,65,68,69,91] Evidence of the association between bone fracture and lactase deficiency from three studies of 895 postmenopausal women were inconsistent in direction and effect size.[29,68,69] One population-based study "Vantaa 85+" of 601 Finnish elderly found that those with C/C genotype (lactase deficient) had more than a threefold increase in crude odds of hip and nearly a twofold increase in crude odds of wrist fracture when compared to TT genotype (lactase persistent and reporting lower odds of milk aversion).[65] The Austrian Study Group on Normative Values on Bone Metabolism did not find a significant association between genetic polymorphism and bone fracture in elderly men.[91]

Lactose intolerance: One study reported that children who avoided drinking cow's milk because of perceived milk intolerance did not have higher rates of fracture compared to milk avoiders who did not report symptoms of intolerance.[89] Finnish postmenopausal women with lactose intolerance (and presumed lower lactose intake) did not have greater risk of any, vertebral, or nonvertebral fracture when compared to healthy women.[29] Austrian men and women with self-reported symptoms of LI (and presumed lower lactose intake) during the

hydrogen breath test had a 96 percent increase in crude odds of any fracture.[92] Estonian men and women with self-reported milk intolerance had increased crude odds of osteoporotic fracture.[67]

Association between lactose intake and osteopenia, osteoporosis, bone mineral density, and bone mineral content. Low level evidence indicates that adults with lactose free or low lactose diets had osteopenia more often than controls.[5,93,94] Postmenopausal Taiwanese women consuming lactose free diets had a twofold increase in adjusted odds of femoral neck osteopenia compared to nonvegan vegetarians.[93] Italian adults with symptoms of LI and positive hydrogen test (assumed to consume low lactose diets) had a large increase in crude odds of osteopenia.[5] Women with different lactase genetic polymorphism (assumed to vary in lactose intake according to lactase gene presence) had the same odds of osteoporosis.[29,69]

Four studies demonstrated that children from Europe,[95] Asia,[96] or New Zealand[76,97] with lactose free or low lactose diets had reduced BMC and BMD.[76,95-97]

Genetic polymorphism. We found low levels evidence that women with C/C genotype (lactase nonpersistent who consumed 48 percent of recommended calcium) had lower BMD compared to TT (lactase persistent) genotype.[68,69] Bone outcomes did not differ by genotype in either gender.[57,67]

Lactose intolerance. We found low levels of evidence that children and adults with self-reported milk intolerance (reduced dairy intake with 45 percent of recommended calcium intake) had reduced BMC and BMD. Children[98] and adolescent girls[99] from the United States with lactose intolerance had an inconsistent reduction in BMC. Adults with self-reported milk intolerance had consistent reduction in BMD[5,67,100] and BMC.[5]

Role of diet: bone health outcomes by intake of dairy and calcium. We found moderate level RCT evidence that increased lactose intake resulted in improved BMC of the lumbar spine and femoral neck in prepubertal children with low baseline milk intake (less than 50 percent of recommended calcium intake). Lactose effects were causal and direct but the effect sized varied across studies and lowered the level of evidence. Dairy intervention with 1,794 or 1,067 mg of calcium per day compared to 400-879 mg of calcium per day for 12 months resulted in a significant increase in total body BMC in boys and girls from Hong Kong.[101] One RCT that included pre-pubertal children with very low baseline milk intake reported significant increases in total body BMC after dairy administration that provided 1,200 mg of calcium per day.[102] The effect, however, was not significant at 18 months of followup.[102] The U.S.[103] and British[104] RCTs that included only girls consuming half of the recommended daily calcium did not demonstrate significant improvement in total body BMC. Study design, population, race/ethnicity, gender, and baseline milk intake could explain inconsistency between studies in lumbar spine BMC. Lumbar spine BMC was increased in three RCTs,[101,102,105] while two trials did not report significant changes.[106,107] Children from Hong Kong with very low baseline calcium intake had the greatest increase in lumbar spine BMC.[101] Dairy intervention increased lumbar spine BMC in girls[105] but not in boys.[106] The improvement in bone mineral density was less evident. Dairy interventions did not increase BMD in girls in two RCTs that reported absolute levels of the outcome.[103,105] Dairy interventions increased BMD from baseline in one RCT of Finnish girls,[107] while British girls[104] and children from New Zealand[102] or Hong Kong[101] did not have significant changes in BMD. Dairy intervention did not result in a significant increase in total spine BMD at 6 months in young women.[62] In one small RCT (n=59) of premenopausal U.S. women, dairy intervention reduced age-related decline over a 3-year period in vertebral BMD.[63] Observational studies reported that children with very low milk intake had reduced BMD when compared to the reference population.[76,96,97] Long term milk avoiders had lower BMC.[76,95-97]

Key Question 3: What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?

Twenty-eight randomized crossover trials were included. Half of the trials included lactose digesting controls. The vast majority of studies of LI were small (<30 subjects) with trial populations ranging between six and 150 subjects. Women constituted 55 percent of the subjects, and the mean age was 37 years (20 studies reporting). Seven trials included children or adolescents, four exclusively. Among the 20 studies reporting race or ethnicity, 33 percent of the subjects were white, 30 percent Hispanic, 20 percent black, and ten percent Asian. Studies did not report outcomes stratified by these baseline factors. In 11 studies abdominal symptoms compatible with malabsorption of lactose prior to study entry were not required for participation. Lactose malabsorption was diagnosed following lactose tolerance tests by the hydrogen breath test in 13 of the studies,[108-120] and blood glucose test in 11 studies.[121-131] Diagnosis based on urinary galactose concentration was reported in one study[132] and biochemical method of diagnosis was not reported in three trials.[133-135] Half of the trials included lactose digesting controls.[110-113,116,120,122,125-129,133,135]

While subjects were routinely tested for LM, only a few studies then tested the intolerant subjects in blinded fashion with increasing doses of lactose administered throughout the day to determine the daily tolerable dosage of lactose. Most studies utilized a single dose of lactose and a lactose-free control administered in water or milk without food, frequently in not totally blinded fashion (i.e., the taste of low lactose milk differs from milk). The statistical rating of symptoms may not indicate clinical significance. The probability that a given dose of lactose induces more symptoms than the control treatment has been assessed by standard statistical tests of the differences between group means. No attention has been paid to the possibility of outliers. Results were heterogeneous in terms of patient populations, interventions, assessment methods, and outcome definitions, thus precluding pooling. Most studies used hydrogen H_2 breath testing to identify lactose malabsorbers which can incorrectly classify subjects. The problem is compounded because studies do not clearly distinguish between individuals with and without symptoms, suggestive of LI individuals who undergo the testing.

The one study that investigated symptoms when lactose was ingested for 1 week with each of the three meals showed that up to 70 grams of lactose/day could be tolerated without appreciable symptoms.[118] Studies testing the tolerance of lactose malabsorbing subjects to a single dose of lactose yielded discordant results. Several studies indicated that subjects with “lactose intolerance” can ingest from 10-15 grams of lactose (comparable to approximately one cup of milk), particularly if taken with food, with no or minor symptoms.[113,116,119,120,126,127,130,131,134,135] When the dosage of lactose was increased to 18-25 grams, once again, the finding of intolerance varied between studies. Five trials reported that intolerance becomes more prominent, with single doses of 20 grams or greater usually yielding appreciable symptoms.[119,127,129,130,134] Lactose may be better tolerated when ingested with other nutrients versus administration of an aqueous solution of lactose or milk as a single test dose without other nutrients. When taken with other nutrients, symptoms appear to be minimal with daily lactose dosages of less than 20 grams (1. 7 cups of milk), while many subjects experience severe symptoms with dosages of 50 grams. In contrast, when lactose/milk is administered as a single test dose without other nutrients, dosages of 12 grams may be symptomatic. Two trials demonstrated that if 20-24 grams of lactose is distributed throughout the day and given with meals, many lactose malabsorbers will tolerate this dosage.[111,132] Studies with comparable lactose doses reporting high frequency of appreciable

intolerance symptoms supplied lactose in a single dose without food.[124,133,134] No studies determined if lactose malabsorbers of differing ethnicities have differing tolerance to lactose. Likewise, there was no data on the relationship of age or sex to the quantity of lactose that can be tolerated by lactose intolerant subjects.

Key Question 4: What strategies are effective in managing individuals with diagnosed lactose intolerance?

For individuals wishing to consume milk and milk products that exceed the amount of lactose that they are able to tolerate, we examined the strategy of consuming lactose reduced/hydrolyzed formulations. A total of 37 unique randomized studies (26 on lactase/lactose hydrolyzed milk supplements and lactose reduced milk, eight on probiotics, two on incremental lactose dose for colonic adaptation, and one on other agents) met inclusion criteria. The quality of the studies was low, with almost no study reporting adequate allocation concealment. Generally, studies had small sample sizes, and reporting of symptoms was variable or not reported: composite scores of four to five symptoms or individual symptoms such as abdominal pain, diarrhea, bloating, and flatulence were reported, either as means or proportion.

Lactase/lactose hydrolyzed milk. The 26 articles represented 28 unique trials. There was one study representing two trials that tested lactase supplements Lactodigest, DairyEase, and Lactaid,[136] while the remaining 25 studies reported on lactose reduced or hydrolyzed milk by adding a lactase enzyme such as beta-galactosidase to the milk. Studies enrolled between six and 150 subjects. Women constituted 56 percent of the subjects (n=23 studies). The mean age of subjects was 37 years of age with a range between 10 and 77 (n=19 studies). Six trials included children or adolescents.[109,114,123,126,127,135] One trial enrolled elderly subjects (mean age 77 years).[116] Within the 19 studies reporting race or ethnicity, 40 percent of the subjects were white, 30 percent Hispanic, 20 percent black, and 9 percent Asian.[109-116,123,126-130,133-135,137] Sixteen studies utilized commercial lactase products or hydrolyzed milk,[108-111,113-115,121-125,128,130,133,135] two used milk products with lactose removed by ultrafiltration or chromatographically,[112,134] and three assessed nonlactose solutions.[116,126,127]

Unclear or unreported methods of lactose removal were noted in two trials.[129,132] Subjects in 18 studies reported abdominal symptoms compatible with malabsorption of lactose prior to study entry.[108-114,121,123-125,128,130,132,134,136-138] Abdominal symptoms were not required for study participation (based solely on biochemical diagnosis) or subjects were not reported to experience symptoms following ingestion of lactose in ten studies.[115,116,122,126,127,129,130,133,135,136] LM was diagnosed following lactose tolerance tests by the hydrogen H_2 breath test in 11 of the studies[108-116,136] and blood glucose test in 13 studies.[121-130,137,138] Diagnosis based on urinary galactose concentration was reported in one study[132] and biochemical method of diagnosis was not reported in three trials.[133-135] Over half the trials included lactose digesting controls.[110-113,116,122,125-129,133,135,137] Among the 18 studies that enrolled symptomatic subjects at baseline, 13 utilized lactose doses greater than 12 grams, comparable to one cup of milk.[108,110,111,114,121,123-125,128,130,132,134,136,137] Hydrolyzed lactose doses typically ranged from 0-2 grams per dose. In most of the studies, the lactose dose was consumed in a single serving. In six trials, the lactose dose was administered over multiple intervals per day for at least part of the study.[110,111,122,125,128,132]

We found insufficient evidence that lactose reduced solution/milk, with lactose content of 0-2 grams, reduced symptoms of lactose intolerance. Seven studies, representing nine comparisons that enrolled individuals who had symptoms compatible with LI reported inconsistent results that

lactose reduced preparations decreased overall symptom scores compared to controls. None of the four studies reported a significant improvement in overall symptoms compared to control preparations of up to 12 grams of lactose. However, as noted in key question 3, doses of 12 grams of lactose or less are well tolerated and produce minimal to no symptoms. When compared to controls given greater than 12 grams of lactose, only two out of five trials reported statistically significant reductions in overall symptoms with lactose reduced/hydrolyzed milk. Results for individual symptoms of abdominal pain, diarrhea, flatulence, and bloating were also inconsistent.

When we examined all included studies, regardless of symptom history, we found insufficient information from 16 (19 comparisons), mostly low quality, trials regarding the effect of hydrolyzed milk, lactase, or non-lactose preparations in reducing GI symptoms compared to lactose controls. Because these studies enrolled subjects with and without a prior history of GI symptoms compatible with LI (and did not provide results stratified by prior symptom history) they have very low applicability to the question to be addressed. Some studies did report substantial reductions (improvement from moderate and severe to mild or none, or an absolute reduction of at least 50 percent) in abdominal pain/cramping[109,112,123,125,134] and diarrhea[136] with use of lactose reduced solution/milk, with lactose content of 0-2 grams, compared to a lactose dose of 12 grams or more. However, even in studies where symptoms were reduced statistically significant reductions were not consistently observed among all symptoms reported, or only a subset of symptoms were reported. For example, the overall symptom score was significantly reduced by 60 percent with 591 milliliters (ml) of lactose reduced milk containing 7.5 grams of lactose compared to a similar amount of milk with 30 grams of lactose[130] and by 13 percent with low lactose skim milk with 0.8-6.5 grams of lactose compared to skim milk with 6.1-49 grams of lactose,[122] but the subjects in both studies were not symptomatic at enrollment, and improvement in individual symptoms was not provided. Mean and total symptom scores were also reduced, from 3.7 to 0.36 with 70 percent hydrolyzed milk compared to placebo with 20 grams of lactose,[108] but subjects were also not symptomatic at enrollment, and improvement in individual symptoms was not provided. One study reported a score of 46 for skim milk with 11.3 grams of lactose, which was reduced to a score of 17 with low lactose milk with 3.2 grams of lactose, but the difference was not statistically significant.[134] Similar reductions were seen in summed scores for abdominal pain from 43 with milk containing 25 grams of lactose to 1 with lactose hydrolyzed milk containing 1.25 grams of lactose[123] and a mean score for abdominal pain from 7.5 with milk containing 12 grams of lactose to 4.1 with milk containing lactase,[109] both in children. Again, neither study required subjects to be symptomatic at baseline. One study showed a statistically significant reduction in abdominal pain from moderate to none or mild with low lactose milk containing 2.9 grams of lactose compared to skim milk containing 28.5 grams of lactose.[125] One trial found a significantly greater percentage of subjects reporting abdominal pain and bloating compared to the 0.5 gram and 1.5 gram doses, respectively.[112] Compared to placebo, use of lactase supplement Lactodigest, DairyEase, or Lactaid in doses of two to four capsules/tablets when taken with 400 ml of 2 percent milk containing 20 grams of lactose reduced overall symptom scores in subjects not symptomatic at enrollment. However, more relevant to the clinical question of treatment for individuals with symptoms compatible with LI who desire to consume lactose beyond the "minimally tolerable dose," these products did not reduce symptoms when administered with a dose of 50 grams of lactose in subjects who had symptoms compatible with LI.[136] Generally, studies had small sample sizes and reporting of symptoms was variable: composite scores of four to five symptoms or individual symptoms such

as abdominal pain, diarrhea, bloating, and flatulence were reported, either as means or proportion, making pooling estimates difficult.

Prebiotics and probiotics. Trials were generally small, enrolling between nine and 28 subjects. Among the five studies reporting gender, women constituted 34 percent of the subjects.[139-143] Two studies enrolled only male subjects.[142,143] Subjects were typically young to middle-aged adults (between 18 and 45 years old), and only one study enrolled subjects older than 60 years of age.[144] Half of the studies reported race or ethnicity. White subjects comprised two trials,[140,141] one study evaluated black African immigrants to France[142] and one trial was conducted in Taiwan.[117] Five of the studies were conducted in the United States,[139,140,143-145] and two in France.[141,142] Five trials assessed probiotic test products, prepared by adding strains of lactobacillus acidophilus, lactobacillus bulgaricus, or bifidobacterium longum to milk prior to consumption.[117,139,140,144,145] Four studies evaluated yogurt products.[141-143,145] Lactose malabsorption was diagnosed by the hydrogen breath test in all studies.

We found insufficient evidence to determine the effectiveness of yogurt or probiotics to improve LI symptoms. The inclusion criteria were variable; the type, source, and concentration of yogurt and probiotics studied were variable; and no two studies studied the same agent. Results either did not show a difference in symptom score or reported clinically insignificant differences, mostly in symptoms of flatulence. Symptoms of abdominal pain, diarrhea, or overall score were not improved, which may be more clinically relevant to the patients and their providers. Only one study noted that the enrolled subjects reported symptoms compatible with malabsorption of lactose prior to study entry[144] and reported a symptom score of 40 in groups given milk or acidophilus milk. In the remaining studies, study entry was based solely on hydrogen H_2 breath tests, and subjects were not reported to experience symptoms following ingestion of lactose. Lactose doses in the control tests were between 10 and 20 grams. Overall symptom score was reduced from 12.5 with 2 percent milk containing 20 grams of lactose to 2.8 with the same milk formulation but with added lactobacillus at 10^9 cfu/ml[117] and from fairly strong to mild with 400 ml of bulgofilus milk (Ofilus bacteria+L. bulgaircus) compared to control (10 grams lactulose in 250 ml water), both with 18 grams of lactose.[141] Reductions in other symptoms, such as abdominal pain and diarrhea, were either not reported, not significantly different, or of lower clinical significance or relevance. The inclusion criteria were variable, the type, source, and concentration of yogurt and probiotics studied were variable, and no two studies studied the same agent.

Other strategies. We identified three small short-term studies.[118,146,147] We found insufficient evidence that incremental doses of lactose reduce LI symptoms. We found one cross-over study evaluating 10 days of incremental doses of lactose versus dextrose for colonic adaptation among 20 subjects with LM diagnosed on hydrogen breath tests.[118] Most subjects had mild symptoms, even with high doses of lactose consumption. Flatulence but not abdominal pain and diarrhea were reduced. The second study evaluated colonic adaptation to lactose by comparing symptoms among 46 adults with lactose malabsorption that were fed either 34 grams of lactose or sucrose in a double blind fashion for 13 days.[146] The overall clinical score and individual mean scores for pain, flatulence, bloating, and borborygmi also improved, but the improvement seen in lactose and sucrose groups was similar, suggesting a placebo response. One additional study of 40 subjects with malabsorption on breath hydrogen testing evaluated rifaximin compared to lactose free diets and placebo.[147] Rifaximin and lactose free diets resulted in similar reductions in abdominal pain, diarrhea, bloating, and distension compared to their respective baseline values. There were no data directly comparing rifaximin to placebo or lactose-free diets.

Summary and Discussion

Our evidence synthesis reached the following major conclusions: (1) Reliable estimates of prevalence rates for LI in the United States are not currently available, though there is some evidence that the magnitude of LI will be very low in young children and remain low into adulthood for most populations of Northern European descent. For African American, Hispanic, Asian, and American Indian populations the rates of LI will likely be higher in late childhood and adulthood. (2) Evidence regarding the effect of dairy exclusion diets on long-term GI and bone health outcomes is relatively sparse in quantity and low in quality. Evidence does not strongly indicate that dairy-free diets are independently associated with poor long-term bone health outcomes, and there is no direct information on long-term GI outcomes among individuals consuming dairy-free diets. However, results from genetic association tests consistently reported decreased consumption of milk in adults with the C/C genotype compared to those with at least one T allele, suggesting that individuals with lactase nonpersistence avoid milk, presumably to reduce dairy induced GI symptoms. (3) The majority of individuals diagnosed with LI can likely tolerate up to 12 grams (equivalent to 1 cup of milk) at a given sitting with minimal to no symptoms, especially if consumed with other foods. (4) Treatment with lactose reduced milk products may result in clinically important improvements in selected GI symptoms in selected individuals diagnosed with LI or LM, but there is very little high quality data on the effect of incremental lactose loads.

Our findings have important research and clinical implications. With regard to LI prevalence estimates, most of the identified research assessed subjective symptoms in an unblinded fashion or an inability of individuals to fully absorb lactose irrespective of symptoms or lactase nonpersistence. Available data tended to be from highly selected populations and not likely representative of the overall U.S. population. Additional genetic association studies may provide a useful method to assess LI in epidemiologic studies. Dietary history assessing dairy consumption and symptoms linked to results from testing for the lactase gene might obviate the need for blinding of lactose intake.

Our findings that there is not a strong or consistent association on bone health with dairy intake is supported by a previous evidence report that concluded that the majority of findings concerning vitamin D, calcium, or a combination of both nutrients on the different health outcomes (including bone health) were inconsistent. Because the major long-term health concern of dairy exclusion diets is the potential for intake of calcium below recommended dietary levels, future research is required to clarify whether populations that consume dairy-free diets have adverse bone health outcomes, particularly fractures. We found that dairy interventions in healthy children with low baseline milk intakes may result in short but not long-term improvement of bone mineral content and density. Adults with lactose free or low lactose diet may have increased risk of bone fractures. Low and inconsistent evidence suggested that adults with milk intolerance and malabsorption had greater odds of fractures and worse bone outcomes. Adult women with low childhood and lifetime milk intake, lactose malabsorption, and C/C genotype had greater risk of osteoporosis and fractures. However, studies did not find significant association with lactose metabolism and bone health in men. There was little data on African Americans. Additional information would be important because African Americans have a higher prevalence of LI and likely lower consumption of dairy products, yet they have lower rates of bone health outcomes of interest for this report. Children with low baseline calcium

consumption may benefit from increased lactose intake. It is not clear if increased milk consumption in healthy adult women with low childhood and lifetime milk intake, LM, or C/C genotype reduces the risk of osteoporosis and fractures.

Our findings can aid patients and practitioners in clinical management of individuals diagnosed with lactose intolerance. The preponderance of evidence indicates individuals diagnosed with LI can be informed that they can ingest 12 grams of lactose (1 cup of milk) as a single dose (particularly if taken with food) with no or minor symptoms. Therefore, most individuals (either self or clinically diagnosed) can consume a sufficient amount of dairy products each day to meet minimum recommendations without incurring GI symptoms. However, as the dose is increased above 12 grams, these individuals can be informed that intolerance becomes more prominent, with single doses of 24 grams usually yielding appreciable symptoms. There is some evidence that if 24 grams of lactose are distributed throughout the day, many lactose malabsorbers will tolerate this dosage. Lactose in a dose of 50 grams induces symptoms in the vast majority of subjects. No studies assessed if lactose malabsorbers of differing ethnicities have differing tolerance to lactose. There was no data on the relationship of age or sex to the quantity of lactose that can be tolerated.

Advice regarding additional management strategies is hampered from the lack of study uniformity in design and methodology. We caution that the criterion of being symptomatic at baseline was found in only a few studies. This makes comparison of symptoms at the end of trial difficult across studies. Most studies had an 8-hour recording period, and it is difficult to generalize these findings to individuals with chronic relapsing remitting problems with a constellation of symptoms. While it seems logical that consuming lactose reduced products (i.e. to less than 12 grams of lactose) would reduce or prevent LI symptoms, the evidence was insufficient that products, as tested, provide this effect.

Key Question 5: What are the future research needs for understanding and managing lactose intolerance?

We recommend that future prevalence studies be derived from population-based samples that include adequate distributions across ages and ethnic variation in order to assess the effects of these factors. Efforts are needed to account for possible placebo effects in the reporting of symptoms. The best mechanisms available for accounting for placebo effects would be to conduct blinded challenges with and without lactose and to assign the difference in reported symptoms as the true prevalence due to the lactose challenge. Double blind placebo controlled RCTs of individuals examining the effect of treatment strategies that enroll subjects with clearly documented LI are needed. Standardized, validated outcome reports are needed. Additional work on what constitutes a meaningful challenge dose should also be conducted. We recommend that research on lactose intolerance take into account the prevalence of symptoms that might be expected following doses of lactose that would be consumed during a normal diet (e.g., 1 cup or 12 grams) as compared to extreme doses of lactose that are comparable to getting a full day's worth of calcium from a one-time consumption of milk (50 gram load at a single sitting).

We recommend that future research investigate the association between lactose and dietary calcium intake and patient outcomes in patients with lactose intolerance lactose free diet compared to age, gender, and race/ethnicity matched controls. We recommend that the sources of dietary calcium from nondairy products and from nutritional supplements be examined separately and in interaction with other dietary patterns (food synergy).[148-150] Bone health in

treated patients with LI is unknown. Length and doses of dairy products, probiotics, and plant calcium sources, as well as patient adherence to the recommended treatment regimes may modify the association and should be examined in future research. We recommend that future studies examine intermediate outcomes such as improvement in bone density and mineral content but, more importantly, clinical outcomes such as the incidence of osteoporosis and fractures. We recommend that other health outcomes include obesity, diabetes, cardiovascular diseases, and cancer in treated and untreated lactose intolerant patients in comparison with the general population.

Additional studies are required to accurately diagnose the overlapping symptoms of LI from other GI disorders (especially IBS), determine the health consequences of low lactose diets, and identify methods to improve patient and provider information about the diagnosis and management of LI versus other GI symptom based conditions (especially functional bowel or celiac disease) versus LM.

It is not clear to what extent restriction in intake of milk is from symptoms of LI versus reasons unrelated to symptoms, such as taste, caloric intake, or cultural factors. To the extent that milk avoidance is unrelated to LI, lactose reduced milk is not going to enhance ingestion. Thus, we believe a crucial question is to determine to what extent symptoms of LI limit the ingestion of milk or milk related products. Information on this could be obtained by studies in which lactose malabsorbers to avoid milk are provided with lactose containing and lactose hydrolyzed diets to determine if ingestion of milk and milk related products is increased by reduction of lactose content. To the extent that milk intake is reduced due to lactose intolerance symptoms, the next important question to answer is if there are long-term health consequences of limiting lactose intake.

Evidence Report

Chapter 1. Introduction

Milk and milk products contain high concentrations of the disaccharide lactose (galactose and glucose linked by a beta-galactoside bond). Intestinal absorption of lactose requires that the disaccharide be hydrolyzed to its component monosaccharides, both of which are rapidly transported across the small bowel mucosa. A brush border beta-galactosidase, lactase, carries out this hydrolysis. While infants virtually always have high concentrations of lactase, sometime after weaning a genetically programmed reduction in lactase synthesis results in very low lactase activity in some adult subjects, a situation known as lactase nonpersistence.

Lactase nonpersistence results in incomplete digestion of an ingested load of lactose, hence lactose is malabsorbed and reaches the colon. If sufficient lactose enters the colon, the subject may experience symptoms of abdominal pain, bloating, excess flatulence, and diarrhea, a condition known as lactose intolerance (LI). Diseases of the small bowel mucosa (infection, celiac disease) may also be associated with low brush border lactase, with resultant lactose malabsorption (LM) and LI.

The terminology involved in lactose absorption/intolerance is as follows:

a) Lactase nonpersistence (or lactase insufficiency) – indicates that brush border lactase activity is only a small fraction of the infantile level, a condition documented by analysis of brush border biopsies. Recently it has been shown that a genotype (C/C) of the lactase promoter gene is responsible for lactase nonpersistence, and demonstration of this genotype can be used as indirect evidence of lactase nonpersistence.
b) Lactose malabsorption – indicates that a sizable fraction of a dosage of lactose is not absorbed in the small bowel and thus is delivered to the colon. Since such malabsorption is virtually always a result of low levels of lactase, there is a nearly one to one relationship of lactase nonpersistence (or deficiency) and LM. LM is objectively demonstrated via measurements of breath H_2 or blood glucose concentrations following ingestion of a lactose load.
c) Lactose intolerance – indicates that malabsorbed lactose produces symptoms (diarrhea, abdominal discomfort, flatulence, or bloating). It should be stressed that this symptomatic response to LM is linked to the quantity of lactose malabsorbed (as well as other variables), i.e., ingestion of limited quantities of lactose does not cause recognizable symptoms in lactose malabsorbers, while very large doses commonly induce appreciable LI symptoms. As a result, the prevalence of lactase nonpersistence or LM could far exceed the prevalence of LI symptoms in population groups ingesting modest quantities of lactose.

A public health problem may arise when large numbers of individuals diagnose themselves as being lactose intolerant. However, these self-identified lactose intolerant individuals may actually be lactase persisters. Some of these lactase persisters (and even lactase nonpersisters) may mistakenly ascribe the symptoms of undiagnosed irritable bowel syndrome (IBS) or other intestinal disorders to LI. Given that the relatively nonspecific abdominal symptoms caused by IBS and lactose malabsorption are extremely susceptible to the placebo effect, reliable demonstration of LI requires double-blind methodology.

The problem may become intergenerational when self-diagnosed lactose intolerant parents place their children on lactose restricted diets (even in the absence of symptoms) or use

Appendixes and evidence tables cited in this report are available at http://www.ahrq.gov/downloads/pub/evidence/pdf/lactoseint/lactint.pdf.

enzymatic replacement in the belief that the condition is hereditary. Children and adults with lactose intolerance may avoid dietary milk intake to reduce symptoms of intolerance. Since the avoidance of milk and milk containing products can result in a dietary calcium intake that is below recommended levels of 1,000 milligrams (mg) per day for men and women and 1,300 mg for adolescents, osteoporosis and associated fractures secondary to inadequate dietary calcium is the perceived major potential health problem associated with real or assumed lactose intolerance.

Current dietary recommendations suggest consuming 3 cups/day of fat-free or low-fat milk or equivalent milk products. This amount is equivalent to about 50 grams of lactose, which we defined to be the threshold of minimum tolerance. We defined LI to be present when ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject induces gastrointestinal (GI) symptoms not observed when the subject ingests an indistinguishable placebo.

Because ingesting smaller portions over the course of the day may minimize potential problems with larger acute lactose loads, the above definition of LI may miss lactose malabsorbers who ingest smaller dosages of lactose. The prevalence of clinically important LI requires demonstration that the quantity of lactose that subjects actually ingest (or wish to ingest) causes symptoms in placebo controlled experiments.

Treatment to reduce lactose exposure, while maintaining calcium intake from dairy products, consists of a lactose restricted diet or the use of milk in which the lactose has been pre-hydrolyzed via treatment with lactase supplements. Lactase supplements taken at the time of milk ingestion also are commercially available.

This report was commissioned as background material for a National Institutes of Health (NIH) and Office of Medical Applications of Research (OMAR) Consensus Development Conference on Lactose Intolerance and Health to address the following key questions:

Understanding the terminology of lactose-related “problems” is important and outlined as follows:

1. Lactase deficiency – low concentrations of lactase in the small intestinal brush border relative to the concentrations observed in infants.
2. Lactose malabsorption – failure of the small bowel to absorb the bulk of an ingested load of lactose.
3. Lactose intolerance – a symptomatic response to malabsorption of lactose.

Lactase Deficiency

There are multiple causes of lactase deficiency. Congenital lactase deficiency, a very rare condition in which lactase synthesis is negligible at birth, results from the inheritance of two defective alleles of the lactase transcribing gene located on chromosome 2. Secondary lactase deficiency occurs in diseases that damage the brush border, such as celiac disease or intestinal infections. This deficiency usually is reversible with recovery from the disease. Lactase nonpersistence is a condition in which lactase synthesis is normal at birth and throughout infancy. However, after weaning, lactase synthesis declines, and by adulthood brush border lactase concentrations are only about 10 percent of the infantile level. This nonpersistence of lactase synthesis, which occurs despite continued exposure to milk or lactose, is present in about 70 percent of the world’s adult population. This review will focus solely on the problems associated with lactase nonpersistence.

Lactase nonpersistence versus persistence has been shown to be a function of a lactose promoter region located upstream from the lactase gene. In lactose nonpersistent subjects the activity of this promoter is programmed to decline markedly after weaning, with a resultant decline in lactase synthesis. Several population groups, most prominently individuals of northern European extraction, have mutations of this promoter which permits it to remain active throughout life. In northern Europeans, a single nucleotide thymine for cytosine substitution in the promoter region allows this gene to retain activity throughout adulthood with resultant lactase persistence. Lactose nonpersisters have a C/C genotype whereas persisters have a C/T or T/T genotype (the C→T mutation is a dominant trait).

Direct assessment of brush border lactase levels requires analysis of biopsies of small bowel mucosa via either measurement of enzymatic activity or histochemical staining for lactase. Genetic assessment of the C/T promoter area recently has become available. The complexity and expense of these techniques has limited their application, and information concerning the lactase nonpersistence/persistence state of individuals largely has been inferred from measurements of lactose absorption. The Digestive Diseases Clearinghouse of the National Institute of Diabetes, Digestive and Kidney Diseases states that 30 million to 50 million individuals in this country and about 4 billion people worldwide are lactase nonpersisters. Many of these individuals belong to minority groups such as Asians, African Americans, Hispanics, Native Americans, Alaskan Natives, and Pacific Islanders. However, lactase nonpersistence is also observed in a sizable fraction of Caucasians of southern European and Mediterranean origin.

Lactose Malabsorption

Multiple tests have been employed to assess the ability of a subject to absorb lactose. Such testing initially employed measurements of the rise in blood glucose observed after ingestion of a large (50 gram) dose of lactose, the lactose content of one quart of cow's milk. A rise of blood glucose of <20 mg was used as evidence of lactose malabsorption. This test largely has been supplanted by the hydrogen H_2 breath test, which assesses breath H_2 concentration following ingestion of a 50 gram dose of lactose. A rise in breath H_2 signifies that lactose has reached the colonic bacteria and hence was malabsorbed. Various lactose dosages, times of breath collection, and breath H_2 increases have been employed in this test, and the accuracy of hydrogen H_2 breath testing for lactose malabsorption has never been precisely determined. Nevertheless, this simple noninvasive test has been widely employed and much of our knowledge concerning the prevalence of lactose malabsorption in various population groups, as well as the ability of individual patients to absorb lactose, has been obtained via hydrogen H_2 breath testing.

Lactose Intolerance

Lactose intolerance indicates that malabsorption of lactose results in symptoms of diarrhea, flatulence, bloating, or abdominal discomfort. While LM and LI frequently are used interchangeably, the demonstration that an individual malabsorbs lactose does not necessarily indicate that the subject will be symptomatic. The likelihood that a lactose malabsorber will perceive symptoms after ingestion of lactose is a function of many variables, including the dosage of lactose, lactase activity of the mucosa, foods co-ingested with lactose, the lactose fermentation pathways of the colonic flora, and the sensitivity of an individual's colon to lactose malabsorption. Of particular importance is the dosage of lactose. Intolerance to supra-

physiological loads of lactose (such as were employed in the lactose tolerance test) does not necessarily indicate that subjects will be symptomatic with a smaller, more physiological dosage. Thus, the dosage of lactose that causes symptoms is a major consideration in determining the importance of lactose as a clinical problem. Another important question is the extent to which the colon of select individuals might be particularly sensitive to lactose and/or its bacterial metabolites; e.g., are patients with IBS unusually susceptible to lactose induced symptoms?

Treatment of Lactose Intolerance

LI may be self-diagnosed or diagnosed by a clinician based on historical information and/or the demonstration of lactose malabsorption. Blinded evaluation to document the role of lactose in a patient's symptomatology is not employed. As a result, the subject's unblinded response to a reduction in lactose intake is the standard means of establishing the diagnosis of lactose intolerance. Treatment to reduce lactose exposure consists of a lactose restricted diet or the use of lactase supplements. The former may involve the avoidance of milk and milk-containing foods or the use of milk in which the lactose has been pre-hydrolyzed via treatment with lactase. Lactase supplements taken at the time of milk ingestion also are commercially available.

Health Outcomes of Dairy Exclusion Diets

As described above, gastrointestinal symptoms are the main presenting clinical symptoms of LI and a major reason that individuals are presumed to be lactose intolerant. In attempts to reduce these symptoms, many exclude dairy from their diet. Others avoid dairy for cultural or health belief reasons (vegans), even if they do not have symptoms of LI. Osteoporosis and associated fractures secondary to inadequate dietary calcium is the perceived major long-term health outcome of interest associated with real or assumed LI, since the avoidance of milk and milk containing products usually results in a dietary calcium intake that is well below recommended levels of 1,000 mg per day for men and women and 1,300 mg for adolescents. Women who are pregnant or breastfeeding need between 1,000 and 1,300 mg of calcium daily. Because dairy foods are the major source of dietary calcium intake (in the absence of supplementation), dietary recommendations suggest consuming 3 cups/day of fat-free or low-fat milk or equivalent milk products. This amount could be ingested over the course of the day (e.g., 1 cup three times per day with each meal) to minimize potential problems with larger acute lactose loads. The recommended calcium intake by age group is shown in Table 1. Table 2 shows examples of calcium content in common foods.

Table 1. Recommended calcium intake by age group

Age Group	Amount of Calcium to Consume Daily, Age Group in Milligrams (mg)
0-6 months	210 mg
7-12 months	270 mg
1-3 years	500 mg
4-8 years	800 mg
9-18 years	1,300 mg
19-50 years	1,000 mg
51-70+ years	1,200 mg

Source: Adapted from *Dietary Reference Intakes, 2004*, Institute of Medicine, National Academy of Sciences.

Table 2. Calcium content in common foods

Nonmilk Products	Calcium Content
Rhubarb, frozen, cooked, 1 cup	348 mg
Sardines, with bone, 3 oz.	325 mg
Spinach, frozen, cooked, 1 cup	291 mg
Salmon, canned, with bone, 3 oz.	181 mg
Soy milk, unfortified, 1 cup	61 mg
Orange, 1 medium	52 mg
Broccoli, raw, 1 cup	41 mg
Pinto beans, cooked, ½ cup	40 mg
Lettuce greens, 1 cup	20 mg
Tuna, white, canned, 3 oz.	12 mg
Milk and Milk Products	
Yogurt, with active and live cultures, plain, low-fat, vitamin D-fortified, 1 cup	415 mg
Milk, reduced fat, vitamin D-fortified, 1 cup	285 mg
Swiss cheese, 1 oz.	224 mg
Cottage cheese, ½ cup	87 mg
Ice cream, ½ cup	84 mg

Source: Adapted from U.S. Department of Agriculture, Agricultural Research Service. 2008. USDA National Nutrient Database for Standard Reference, Release 21.

Tolerable Dose of Lactose

Symptoms induced by lactose malabsorption (lactose intolerance) result from: (a) fluid osmotically "held" in the gut by nonabsorbed lactose and its bacterial metabolites and (b) gases released by the bacterial fermentation of lactose. Thus, unlike an allergic reaction that may be triggered by trivial doses of the allergen, a symptomatic response to LM requires that the mass of lactose reaching the colon be sufficient to hold enough water to induce diarrhea and/or permit gas production of a magnitude that causes abdominal pain, distention, or flatulence. It follows that very low doses of lactose should be tolerated without symptoms, while very large doses should routinely induce symptoms. Defining the dosage that is tolerable in lactose malabsorbers is crucial to determining the clinical importance of LM as well the prevalence of LI.

A variety of physiological differences between individuals indicates that there may be sizable individual differences in the dose of lactose that are tolerated by subjects with LM. Lactase nonpersistent subjects retain a low, but readily measureable, concentration of lactase in the brush border of their small bowel, and intubation studies have shown that these subjects are capable of absorbing variable amounts (mean: about 40 percent) of a 12 gram dose of lactose. The kinetics of this digestion have not been studied, but it seems likely that the 12 gram dose of lactose saturates the digestive activity of the gut, such that the percentage absorption would decline with increasing lactose loads. The tests employed to diagnose LM are qualitative and provide no information on the actual quantity of lactose not absorbed. It is possible that there are appreciable differences in the residual lactase activity of lactase nonpersistent subjects, with resultant sizable differences in their ability to digest and absorb a given dose of lactose. Differences in small bowel transit time (partially a function of gastric emptying) could affect the ability of this limited lactase activity to act on luminal lactose.

If the osmotic load created by nonabsorbed lactose was simply a function of the amount of lactose reaching the colon, the potential for nonabsorbed lactose to increase fecal water and induce diarrhea would be predictable: a gram of lactose is equivalent to 3 mosms and fecal water

is isotonic (about 300 mosm/l). Thus, 12 grams of lactose (36 mosm), the quantity in 1 cup of milk, would osmotically hold 36/300 of a liter of fluid in the lumen or about 120 ml. Normally, humans excrete about 100 ml of fecal water each day, and increasing this quantity by 120 ml would yield a loose stool but not severe diarrhea. However, the vast majority of malabsorbed lactose is fermented by the colonic bacteria to short chain organic acids, which are rapidly taken up by the colonic mucosa. When relatively low amounts of lactose reach the colon, fermentation and subsequent absorption of lactose metabolites may be sufficiently rapid to remove all lactose and its metabolites from the fecal stream, thus protecting the subject from lactose-induced diarrhea. However, as the lactose load increases, the production of bacterial metabolites may outstrip the ability of the colonic mucosa to remove these metabolites. In this situation, bacterial metabolism increases the osmotic load over that of lactose with a resultant increase in fecal volume. Thus, differences in fecal bacterial metabolism, colonic mucosal function, and colonic transit time influence the susceptibility of individual subjects to develop diarrhea following malabsorption of lactose.

Colonic bacteria ferment lactose via gas producing and nongas producing pathways. Adaption of the colonic flora via a shift to nongas producing pathways is considered to be the explanation for the decreased H_2 excretion that occurs following daily exposure to large doses of lactose. This fermentation pathway could reduce the distention and flatulence noted with lactose malabsorption. The quantitatively important gases directly released during fermentation of lactose are carbon dioxide (CO_2) and hydrogen gas (H_2). The third quantitatively important gas resulting from fermentation is methane (CH_4), a product of methanogenic bacteria that utilize preformed H_2 and CO_2 to synthesize CH_4, a reaction that results in a fivefold reduction in gas volume ($1\ CO_2 + 4\ H_2 \rightarrow 2\ H_2O + 1\ CH_4$). In addition, several other bacterial reactions utilize H_2, and H_2 released from fecal material is only a small fraction of that produced. After leaving the feces, CO_2 is very rapidly absorbed across the intestinal mucosa; H_2 and CH_4 are also absorbed, albeit at a slower rate than CO_2. The luminal gases that escape metabolism and absorption are excreted per the anus and thus have the potential to increase flatus volume and frequency. Since there are individual differences in the gas producing and consuming reactions, it would be expected that the volume of luminal gas resulting from malabsorption of a given quantity of lactose might vary widely from one subject to the next.

Lastly, individuals differ in their response to colonic distention. Subjects with a “hypersensitive” colon may rapidly propel nonabsorbed lactose and its metabolites through the colon with resultant diarrhea and flatulence, while slower transit in the less sensitive colon could allow for more complete absorption of the metabolites, hence no diarrhea or flatulence. Similarly, the hypersensitive colon might perceive discomfort with a degree of distention that was imperceptible to subjects with a less sensitive colon.

The above theoretical discussion suggests that there could be wide individual differences in the daily dose of lactose that is tolerable to subjects with lactose nonpersistence. Elucidation of this tolerable dose can only be obtained from a study of the subjective response of subjects to ingestion of known dosages of lactose. Some of the many factors that could influence the results of such studies are:

1. Psychological – The perception of symptoms such as bloating and discomfort resulting from dietary manipulations is very susceptible to psychological factors. Thus, reliable testing requires placebo controlled, double-blind methodology.

2. Form that lactose is administered or restricted – The dietary load of lactose, rather than that of milk, should be manipulated to ensure that intolerance symptoms result from lactose rather than some nonlactose fraction of milk.
3. Timing of lactose ingestion – Distributing lactose ingestion throughout the day very likely results in fewer symptoms than a similar quantity of lactose taken as a single dose.
4. Food co-ingested with lactose – Food co-ingested with lactose would tend to reduce the rate of gastric emptying, which would slow the rate that lactose is presented to the small bowel and, hence, increase the fraction of lactose digested and slow the rate of presentation of unabsorbed lactose to the colon.
5. Amount of lactose routinely ingested in diet – Some studies indicate that chronic ingestion of appreciable doses of lactose increases tolerance to lactose.
6. "Sensitivity" of the colon – Subjects with a "hypersensitive" colon (i.e., IBS subjects) might be more susceptible to lactose-induced symptoms than are subjects who do not have IBS.

Strategies to Manage Individuals with Diagnosed Lactose Intolerance

Lactose is a simple disaccharide composed of glucose and galactose linked by a beta 1,4 bond. Intestinal brush border synthesizes lactase, an enzyme that is able to cleave the beta 1,4 bond. This hydrolysis is required for the intestinal absorption of lactose.

Probiotics are live microorganisms that are ingested to prevent or treat disease. The current definition by the Food and Drug Administration and the World Health Organization is "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host." These microorganisms are a heterogeneous group that are nonpathogenic and have beta-galactosidase or lactase intracellularly and may aid in the digestion of lactose ingested by the host. These microorganisms can be added to food products, such as milk and yogurt, or used as supplements. Examples of commonly used probiotics include lactobacillus, bifidobacterium, and saccharomyces. Enzyme replacement therapy with lactase from nonhuman sources to hydrolyze lactose in another important approach to preventing lactose intolerance. There are multiple commercially available lactase supplements containing variable amounts of beta-galactosidase from a variety of sources. In addition, lactose reduced milk is also available commercially, with lactose content of 5 percent to 90 percent of regular milk.

Probiotics and lactase supplements are often regulated as dietary supplements rather than pharmaceuticals or biological agents. Hence, there is no requirement to demonstrate efficacy, purity, potency, or safety prior to marketing probiotics and supplements. The access to the World Wide Web and direct consumer marketing has inundated the public with promotional information, while scientific evidence to support use has been largely overlooked.

Another approach in management of lactose intolerance is to increase the lactose load steadily in one's diet, giving the colon time to adapt. This is supported by the observation that introduction of lactose to diet causes temporary and transient symptoms in individuals.[49] Since lactase from intestinal brush border is not an inducible enzyme, the reduction in symptoms may be explained by colonic adaptation. The time frame is approximately 1 week, as shown by Perman et al.[151] that demonstrated increased beta-galactosidase activity and lactulose catabolism in the feces of healthy adults who consumed 40 gm lactulose per day for 1 week.

Other strategies for management of lactose intolerance include gut decontaminating agents and anti-microbials, such as rifaximin.

Key Questions Addressed in this Report

1. What is the prevalence of lactose intolerance? How does this differ by race, ethnicity, and age?
2. What are the health outcomes of dairy exclusion diets?
    - In true lactase nonpersisters.
    - In undiagnosed or self-identified lactose-intolerant individuals.
    - How does this differ by age and ethnicity?
    - Health outcomes to include: Bone health – osteoporosis, fracture, bone density, bone mass; and gastrointestinal symptoms - abdominal pain, diarrhea, nausea, flatulence, bloating.
3. What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?
    - How does this differ by age and ethnicity?
    - What are the diagnostic standards used?
4. What strategies are effective in managing individuals with diagnosed lactose intolerance?
    - Commercially available lactase
    - Prebiotics and probiotics
    - Incremental lactose loads for colonic adaptation
    - Other dietary strategies
5. What are the future research needs for understanding and managing lactose intolerance?

Chapter 2. Methods

Overview

Analytic Framework

We followed the analytic framework (modified from the U.S. Preventive Services Task Force)[8] to determine causality between treatments and patient outcomes and adverse events in patient subpopulations, including age, race, and ethnic subgroups. Probabilities of diagnosis, treatment, and outcomes were analyzed based on the published literature.

Figure 1. Analytic framework

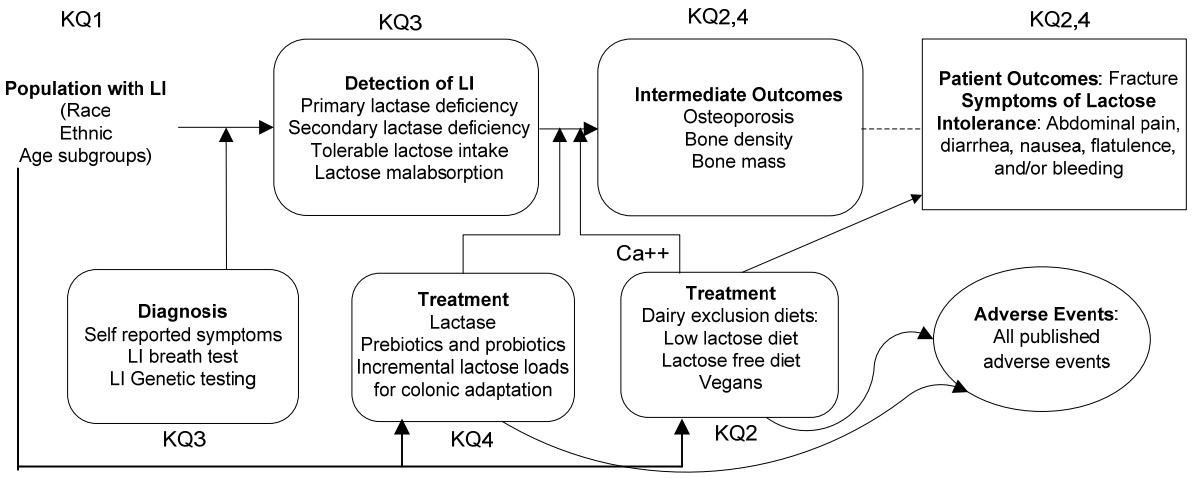


Figure 1 describes target population and also includes individuals with self reported LI (regardless of symptoms) as well as individuals with clinically diagnosed LI, which may include those with lactose malabsorption, lactase nonpersistence, etc. Figure 1 also gives information about research questions:

KQ1. What is the prevalence of lactose intolerance?
KQ2. What are the intermediate and clinical outcomes of lactose free or low lactose diets?
KQ3. What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?
KQ4. What are the intermediate, clinical, and adverse outcomes after treatments for lactose intolerance?

In the clinical situation, a graduated definition of a potentially lactose intolerant subject, might be as follows:

1. The quantity of lactose routinely ingested by the individual that causes symptoms.

Appendixes and evidence tables cited in this report are available at http://www.ahrq.gov/downloads/pub/evidence/pdf/lactoseint/lactint.pdf.

2. The quantity of lactose ingested in some situations by the individual causes the above symptoms.3. The quantity of lactose that the individual would like to ingest (but does not due to fear of symptoms) causes the above symptoms.
4. The quantity of lactose ingested in the course of obtaining 1,500 mg/day of calcium entirely via lactose-containing dairy products causes the above symptoms.

A confounding problem is that factors other than simply the quantity of lactose ingested might influence a subject's symptomatic response, i.e., the form in which lactose is ingested (ice cream versus milk, etc.), the coingestion of nonlactose containing foods, the nonspecificity of symptoms, and the large placebo response potentially observed.

Criteria for Inclusion/Exclusion of Studies in Reviewing and Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

General Inclusion Criteria

We included original observational studies that examined prevalence, symptoms, and outcomes in different age, gender, racial, and ethnic groups; published in the English language; randomized controlled clinical trials (RCTs) that examined different treatment options or doses of lactose loads in patients with LI or LM; and large observational studies in individuals with LI, LM, lactase nonpersistence, or reduced dairy intake that performed at least one strategy to reduce bias. We limited our search to studies published from 1967 to November 2009. We excluded studies that were published in non English languages and small case reports or descriptive case series with less than 100 subjects unless there are no reliable data from other higher quality studies. Because this report is to be used for a U.S. NIH Consensus Conference report we emphasized U.S. based population studies. We excluded populations with other GI disorders, including individuals diagnosed with IBS, inflammatory or infectious bowel diseases, or milk allergies. We excluded children younger than 4 years of age.

Key Question 1: What is the prevalence of lactose intolerance? How does this differ by race, ethnicity, and age?

Study eligibility. We included studies if: (1) they were original research articles, (2) they presented prevalence data related to nonacute LI or LM, including self-reported symptoms, symptoms following a lactose challenge, symptoms following a placebo controlled and blinded lactose challenge, lactose malabsorption via a hydrogen breath test following a lactose challenge, hypolactasia defined by biopsy or genetic tests for adult-type hypolactasia, (3) the study population was not primarily secondary lactose intolerance related to other conditions or treatments, and (4) only results for those greater than 1 year of age. Since the focus of this report is to provide evidence most relevant for a U.S. population, all studies with a sample size greater than 50 that met the previous criteria were included if the study reported results from a U.S.

population. Only larger studies (at least 100 participants) of populations outside of the United States were included.

To the extent that evidence of reliable estimates of LI is missing, we reviewed the evidence of prevalence of lactose malabsorption, lactase nonpersistence (adult-type hypolactasia) and self-reported symptoms following lactose consumption.

Population. We included persons older than 4 years of age.

Conditions. We defined lactose intolerance to be present when ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject induces GI symptoms (abdominal pain, bloating, diarrhea, nausea, flatulence) not observed when the subject ingests an indistinguishable placebo. The 50 gram dose of lactose, the quantity present in a quart of milk, was selected because this quantity of milk provides the maximal recommended daily intake of calcium (1,500 mg), and this dosage approaches the maximal daily volume of milk likely to be ingested by most Americans (http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/). As discussed previously, LI defined in this way does not indicate that intolerance symptoms necessarily will be recognizable when these subjects ingest smaller dosages of lactose (as does the vast majority of the U.S. population). The prevalence of clinically important LI requires demonstration that the quantity of lactose that subjects actually ingest (or wish to ingest) causes symptoms in placebo-controlled experiments. We excluded congenital lactase deficiency, developmental lactase deficiency among pre-term infants, milk allergies commonly seen in infants, and acute lactose intolerance (<30-60 days duration) due to such things as antibiotic use or illness.

Disease severity. Lactose malabsorption is the physiologic problem that manifests as LI and is attributable to an imbalance between the amount of ingested lactose and the capacity for lactase to hydrolyze the disaccharide.[7] LM indicates that a sizable fraction of a dosage of lactose is not absorbed in the small bowel and thus is delivered to the colon. We defined severity of LM according to the amount of consumed lactose (desired or required to meet established dietary needs) before experiencing clinical symptoms of LI. Since such malabsorption virtually always is a result of low levels of lactase, there is a nearly one to one relationship of lactase nonpersistence (or deficiency) and LM. LM is objectively demonstrated via measurements of breath H_2 or blood glucose concentrations following ingestion of a lactose load. We analyzed severity of lactose intolerance according to criteria from diagnostic tests: lactose intolerance breath test: increase from baseline in hydrogen + methane (in parts per million [ppm]) by 20-38 ppm as mild and >39 as severe LI.

We defined lactase nonpersistence according to presence of lactase enzyme on intestinal biopsy and according to the presence of the C/C genotype of the lactase promoter gene with genetic testing using restriction fragment length polymorphism or by DNA Sequencing to detect single-nucleotide polymorphisms (C-13910T, G-22018A) located upstream of the lactase gene within the gene MCM6.

We reviewed differences in prevalence estimates based on different definitions of LI:

- Primary lactase deficiency, a genetically determined decrease or absence of lactase is noted, while all other aspects of both intestinal absorption and brush border enzymes are normal. Primary lactase deficiency is attributable to relative or absolute absence of lactase that develops in childhood at various ages in different racial groups and is the most common cause of LM and LI. Primary lactase deficiency is also referred to as adult-type hypolactasia, lactase nonpersistence, or hereditary lactase deficiency.

- We excluded individuals if secondary lactase deficiency occurs in association with small intestinal mucosal disease with abnormalities in both structure and function of other brush border enzymes and transport processes. Secondary lactase deficiency is often seen in celiac sprue.

Comorbidities, patient demographics. We attempted to review differences in prevalence in individuals of different age groups defined as: Preschool Children: 4-5 years, Children: 6-12 years, Adolescents: 13-18 years, Adults: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, and Elderly Adults: 80 and over.

We attempted to review differences in prevalence of LI in patients of different race-ethnicity groups defined as: Continental Africans, Asians and Europeans, African Americans, Arabs, Caucasians, Arabs, Asian Americans, and Hispanic Americans. We included studies of patients with LI and all comorbidities except acute diseases, treatment of which could cause secondary LI.

Outcomes.

Prevalence of LI. We reported prevalence according to: (a) patient reported diagnosis of LI, (b) clinician diagnosis of LI, and (c) absolute difference in prevalence of individuals with symptoms as derived from randomized controlled blinded trials conducted in subjects diagnosed with LI. We compared outcomes between individuals with a diagnosis of LI receiving blinded lactose (at varying doses) and control interventions, as well as the outcome from blinded RCTs, comparing outcomes in subjects with diagnosed LI versus control subjects. We assessed the prevalence of LM by evaluating studies using breath hydrogen measures.

Glucose tolerance testing is rarely used clinically today, and studies assessing this method for evaluating LM were excluded. Studies assessing only intestinal biopsies were reviewed for quality and applicability.

A critical aspect of this question was to clearly define and differentiate between: (1) lactase nonpersisters, (2) lactose malabsorbers, and (3) lactose intolerance.

LI is the key component of this question and conference. Identifying a gold-standard definition of LI is critical and difficult. There is no objective laboratory test (intestinal biopsies are rarely done and only assess lactase enzyme levels; physiologic tests: e.g., hydrogen breath tests measure LM to a laboratory challenge and need to be evaluated to determine whether they accurately identify clinically relevant LI.

We defined LI to be present when ingestion of 50 grams of lactose (or less) as a single dose by a lactose malabsorbing subject induces gastrointestinal symptoms not observed when the subject ingests an indistinguishable placebo.

We evaluated prevalence according to different populations and methods of assessment with a particular focus on presence or absence of specific symptoms among individuals participating in blinded RCTs evaluating LI. While assessing prevalence in RCTs typically is not done to assess prevalence, we believe that patient reported symptoms and resolution of symptoms in the absence of placebo controlled trials are not reliable.

Key Question 2: What are the health outcomes of dairy exclusion diets?

Population. We included populations that consumed or were likely to consume dairy free or low dairy diets and reported on long-term GI and bone outcomes. We excluded individuals with

irritable bowel syndrome or other GI disorders, such as infectious or inflammatory diarrhea. We excluded populations with children under age 4.

Interventions. We defined dairy exclusion diets as low lactose diets that generally eliminate only milk and milk products or lactose free diets that eliminate all lactose products, including foods that are prepared with milk, both at home and in commercially packaged foods. We included studies with the following comparators: placebo or regular diet. We defined interventions when patients followed lactose free diets prescribed by health care professionals. We defined exposure when subjects followed low lactose or lactose free diets without recommendations from health care professionals. We included indirect evidence of the effect of dairy exclusion on health outcomes by including studies of populations known or suspected of having low dairy intake (e.g., diagnosis of LI/LM, lactase nonpersistence based on intestinal biopsy or genetic test association for lactase nonpersistence) even in the absence of specific documentation of amount of lactose intake. We assessed associations between lactose intake and factors associated with low lactose intake on GI symptoms or bone health, including clinical (fracture) and intermediate outcomes (osteoporosis, bone mineral density, and content).

Outcomes.

Primary bone outcomes. Fracture.

Secondary bone outcomes. Osteoporosis, bone density, bone content.

Primary gastrointestinal outcomes. Abdominal pain, diarrhea, nausea, flatulence, bloating. Osteoporosis was defined according to World Health Organization Criteria[1-3] as a BMD 2.5 standard deviation or more below the young average value in women and men.[4] Osteopenia was defined as a BMD 1-2.5 standard deviation below the population average.[5]

We used reference data on femur bone mineral content and density of noninstitutionalized adults in the United States from the third National Health and Nutrition Examination Survey that collected dual energy x-ray absorptiometry in the nationally representative sample of 14,646 men and women 20 years of age and older.[6]

Adverse events. All published adverse events.

Timing. We included prospective and retrospective studies with duration of followup long enough to detect long-term differences in outcomes (5 years for fractures, 1-2 years for secondary bone outcomes, and greater than 1 month for GI symptoms). We evaluated the impact of lactose exclusion diets on shorter-term (<1 month) patient reported GI symptoms from observational and interventional studies among individuals with both LI and non LI controls. GI outcomes from RCTs with shorter duration followup are reported in Key Questions 3 and 4.

Setting. We included studies in primary and specialty outpatient settings and population based settings.

Co-interventions. We reviewed co-interventions in studies that reported patient outcomes after low lactose and lactose free diets.

We conducted a literature search to identify three types of studies:

1. Studies in patients with LI who followed lactose free diets.
2. Studies that examined patient outcomes among healthy populations consuming dairy exclusion (or very low dairy) diets (e.g., vegans).
3. Meta-analyses and systematic reviews that synthesized the association between dairy (dietary Ca++) intake and patient outcomes.

Confounding factors. We analyzed the adjustment for the known factors that could confound the association between lactose intake and bone health, including age, gender, race, menopausal status in women, external calcium supplementation, renal function, and smoking.

We abstracted how systematic reviews addressed the adjustment for confounding for the association between low milk intake and bone fractures.

The main long-term health concern related to lactose exclusion diets from this report was predominately related to potentially low calcium and vitamin D intake associated with these diets. We also assessed the impact of dietary or supplemental calcium and/or vitamin D. We reviewed whether the studies that examined patient outcomes in association with low dietary milk intake addressed calcium intake from other sources and supplementation with Ca++ or vitamin D. This provided us with contextual information regarding the potential role of low lactose or lactose free diet on bone health independent of other sources of Ca++ or vitamin D.

Key Question 3: What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?

Population. Our target population was limited to subjects with self or clinically diagnosed LI. We focused on populations with clinically diagnosed LI. We defined genetic testing as reference methods to diagnose primary LI. We defined LI breath tests as methods for assessing LM. We defined self reported LI as the presence of self described clinical symptoms occurring only when they ingested lactose and relieved when they eliminated/reduced lactose or used products to hydrolyze lactose prior to ingestion. We quantified the type and severity of symptoms and the amount and type of lactose causing patient reported symptoms. A presumptive working diagnosis of LI was GI symptoms associated with the ingestion of foods containing a quantity of lactose that is either desired by the individual or considered necessary to meet national minimal daily dietary standards, and that resolve upon elimination or marked reduction of these lactose containing foods or when using products to hydrolyze lactose prior to ingestion and return upon lactose rechallenge provided in a blinded fashion. We defined self reporting as index methods to diagnose LI.

Interventions. We evaluated individual daily or weekly intake of lactose stratified by the presence or absence of index diagnostic tests for LI.

Comparators. Placebo, inactive comparator, lactose dose response.

Outcomes.

Primary outcomes. Our primary outcomes included the prevalence and severity of GI symptoms, particularly abdominal pain, diarrhea, nausea, flatulence, and/or bloating. We assessed for the percentage reporting these outcomes as well as scores reported on symptom questionnaires.

Timing. Short term (≤1 month) long-term (>6 months).

Settings. Primary and specialty outpatient settings, population based settings.

Because there was strong evidence of a placebo response, we relied on an evaluation of results from blinded RCTs, including dosing studies to determine the threshold amounts that caused symptoms in subjects with self or clinician diagnosed LI (with or without laboratory evidence of LM) ingesting different doses of lactose versus controls and the outcomes among individuals ingesting lactose with a diagnosis of LI versus non LI controls. Where possible, we attempted to categorize findings according to age, ethnicity, and patient reported baseline LI severity and whether symptoms differed between subjects diagnosed with LI (self versus clinician) and controls.

We characterized the diagnostic standards used in these studies (e.g., patient reported symptoms and breath hydrogen (measure of LM not LI). If there are gaps in evidence related to

amount and type of daily lactose intake, symptoms were defined as patient reported: gas/flatulence, abdominal pain, bloating, and diarrhea.

Key Question 4: What strategies are effective in managing individuals with diagnosed lactose intolerance?

Study inclusion. We included randomized double blind controlled trials that evaluated probiotics, enzyme replacement therapies with lactase from nonhuman sources, administration of lactose reduced milk, and regimes of increases in dietary lactose load for improvement of GI symptoms in individuals with presumed LI or LM.

Population. Subjects with presumed LI, LM, or controls and greater than 4 years of age. We also included double blind randomized trials that enrolled subjects with IBS and LM or LI. These were reported as a separate group. We excluded individuals with presumed IBS alone and other likely causes of acute GI symptoms (e.g., infectious, antibiotic, or inflammatory associated bowel disease).

Interventions. We evaluated the following interventions:

- Commercially available lactase
- Prebiotics and probiotics
- Incremental lactose loads for colonic adaptation
- Other dietary strategies

Comparators. Placebo, usual care, no active treatment, or active control.

Outcomes.

Primary outcomes. Disease specific and overall quality of life.

Secondary outcomes. Frequency and severity of specific GI items of disease specific quality of life questionnaires: abdominal pain, diarrhea, nausea, flatulence, bloating.

Adverse events. We evaluated all published adverse events.

Timing. We analyzed all eligible studies regardless of followup duration.

Settings. We included primary and specialty outpatient settings and population based settings.

Assessment of Methodological Quality of Individual Studies

We rated the quality of studies according to recommendations from the Methods Guide for Comparative Effectiveness Reviews. We used the following ratings of Quality of Individual Studies:

- Well designed and conducted (good; low risk of bias). A study that adheres mostly to the commonly held concepts of high quality, including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
- Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

- Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

We assessed for external validity (applicability) according to the Methods Guide for Comparative Effectiveness Reviews.

Data Synthesis

We summarized evidence into summary tables with qualitative analysis of the results for prevalence of LI by subgroups for Key Question 1. We did not pool results for Key Question 1.We attempted to calculate odds ratio with 95 percent confidence interval (CI) or absolute risk differences from the reported number of events in RCTs as well as the number needed to treat to achieve one event of the outcome if the data are homogeneous enough to permit pooling. All additional calculations were performed at 95 percent confidence levels.

We calculated minimum difference in continuous variables from the reported sample size, means, and standard deviations. We calculated crude odds ratios from the reported number of subjects with and without outcomes among compared categories of exposure. Calculations were performed using STATA software,[152] SAS 9.2,[153] and Meta-analyst software (available at https://research.tufts-nemc.org/metaanalyst/) at the 95 percent confidence level.

Attributable risk was calculated as the outcome events rate in patients exposed to different clinical interventions.[9-11] The number needed to treat to prevent one symptomatic event was calculated as the reciprocal to the absolute risk differences in rates of outcomes events in the active and control groups: 1/(control group event rate - treatment group event rate).[10-12] We did not pool data related to Key Questions 1 or 2.

For Key Questions 3 and 4 if symptoms associated with lactose malabsorption (abdominal pain and frequency of diarrhea) data were appropriate for pooling, they were analyzed using RevMan 5.0 software using a random effects model.[154] Standardized mean differences (symptom effect sizes) were calculated with the generic inverse variance method due to the crossover study design of the trials.

Grading the Evidence for Each Key Question

Assess Study Quality and Strength of Evidence

On the basis of the quality checklist(s) developed for articles relevant to the various key questions, we assigned a quality score to each article. We used methods for assessing study quality and strength of evidence according to the Methods Guide for comparative Effectiveness Reviews that is conceptually similar to the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) system of evidence rating.[13,14] Specifically, we assessed four domains: risk of bias, consistency, directness, and precision. When appropriate, we also include dose response association, presence of confounders that would diminish an observed effect, strength of association, and publication.

Quality of evidence across studies for each outcome. We graded the quality of evidence for primary outcomes across studies as illustrated below:

Overall ranking of evidence.

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Chapter 3. Results

All work was conducted under the guidance of a Technical Expert Panel (TEP), whose members are identified in Appendix A. Figure 2 shows the inclusion/exclusion criteria and number and reasons for study inclusion and exclusion. The search strategies for the research questions are described in Appendix B. Excluded references are shown in Appendix C.

Key Question 1: What is the prevalence of lactose intolerance? How does this differ by race, ethnicity, and age?

Description of Study Characteristics

Our search strategy identified 2,450 articles from abstracts or full articles that were obtained to determine study eligibility. Each article was read by one extractor and was included for further review if the article either appeared to meet the inclusion criteria or if inclusion was uncertain. In cases where inclusion was not obvious, additional review by a senior investigator occurred.

A total of 54 articles met inclusion criteria (Figure 2). These articles include populations from the United States, as well as populations for Northern, Central, and Southern Europe, the Middle East, Central America, South America, Africa, Asia, and Australia. As described in our methods section, we over represented studies from the United States in order to make this review more relevant to U.S. populations. Although the majority of research has occurred outside the United States, our review includes 15 studies from the United States, with a total of 4,817 participants.

Only one randomly selected or population representative study of the United States was identified, and this study only included self reported LI on a questionnaire with no lactose challenge or objective confirmation.[35] The vast majority of studies are convenience samples, which make extrapolation of results to the general public difficult to impossible.

Lactose Intolerance

Symptoms following blinded lactose challenge. We identified no studies in the United States or elsewhere that reported on the prevalence of LI based on our "gold-standard" definition of LI. Since abdominal symptoms can be caused by a large number of factors unrelated to lactose and biases in attributing abdominal symptoms following unblinded challenges of lactose, it is difficult to accurately identify the prevalence of symptoms truly attributable to lactose. This is made even more difficult since studies have rarely tried to obtain samples of participants that are representative of the overall U.S. population. Because of these limitations, we were unable to accurately define the true prevalence of LI or estimate the extent to which the true prevalence of LI differs depending on race/ethnicity or age.

The prevalence of symptoms estimated from studies not using blinded challenges is defined for the remainder of the report as "symptoms" so as to intentionally distinguish these results from the prior mentioned "gold standard" definition of prevalence of LI.

Symptoms following nonblinded lactose challenge. We identified 21 studies that reported LI related symptoms (abdominal pain, bloating, excess flatulence, and diarrhea) following a

Appendixes and evidence tables cited in this report are available at http://www.ahrq.gov/downloads/pub/evidence/pdf/lactoseint/lactint.pdf.

challenge of lactose.[7-28] Detailed information about each of these studies, included in Table 3, is stratified into three different groups based on whether the participants self reported prior LI related symptoms prior to the challenge. Studies include results on a total of 8,174 people from various samples collected on every continent except Antarctica.

There is, however, little data available specifically from the United States to answer this question, and the data that are available offer little information about the overall prevalence of people who would report symptoms of LI if they were given a lactose challenge; moreover, these data are particularly limited for providing information on the impact of race/ethnicity and age on prevalence of symptoms. No U.S. studies from the past 30 years were identified. Four older, U.S. studies of convenience samples were identified.[13,18,26,27] Newcomer reported results on a population of healthy Caucasian volunteers with no history of milk intolerance.[18] This study reported no overall prevalence of symptoms following the lactose challenge, but it did report that all six of the participants with biopsy determined hypolactasia reported symptoms, while only 4 percent (2/57) of participants with normal lactase levels reported symptoms. U.S. studies of healthy volunteers from Texas reported results in adults[26] and children[27] for Hispanic and white non Hispanic participants. In adults, Hispanics were 43 percent more likely to report symptoms following a lactose challenge compared to white non Hispanics (Hispanics 67 percent versus non Hispanics 47 percent).[26] Similarly, in children the rate of symptoms was much higher among Hispanic children (41 percent versus 20 percent in non Hispanic); however, even among Hispanic children, the majority did not experience symptoms and among Hispanic children less than 6 years old symptoms were rare (18 percent).[27] The fourth U.S. study included black (n=69) and white (n=30) children between the ages of 4 and 9 years old.[13] This study provided some information that is consistent with studies reported in other countries, showing the overall frequency of symptoms following a challenge is quite low in young children, but the rate increases with age and is significantly higher in black children compared to white children. Specific estimates of the prevalence in age or race strata are impossible, since confidence intervals were very wide.

Larger and more recent studies have been conducted outside of the United States, and these studies do provide more information, suggesting that there are substantial differences in the prevalence of reported symptoms depending on both the age and ethnicity of the population. These non U.S. populations included a total of nearly 7,260 participants from 16 different countries (Table 3).[7-12,14-17,19-25,28] The results in Table 3 are separated according to whether the primary population does or does not have symptoms at baseline.

Many of the studies only reported symptoms in subgroups of their populations; for example, only in people who had positive breath hydrogen tests (LM) or only in people who reported previously having symptoms. Studies that reported results in people both with and without LM, reported significantly greater frequency of symptoms (typically around twice as high) in those with positive breath hydrogen tests compared to those with negative tests.[11,15,22,25]

Two studies reported doses of approximately 50 grams of lactose versus 12 grams of lactose and found much lower rates of symptoms with lower doses.[15,16] While dose studies were uncommon, these dose results suggest that even among people positive for LM, symptoms might only occur in a minority of people when the dose is approximately one glass of milk. This might be particularly true for young children.[15,16]

Older age is a consistent predictor of increased symptoms following a lactose challenge.[13,16,19,23,28,155] For almost all populations it appears as though very few children younger than 6 experience symptoms following lactose challenges. There was some evidence that children of African or Asian decent may experience increased frequencies of symptoms in

childhood at younger ages compared to other populations, but even these studies still showed that the majority of young children did not experience symptoms.[23,28,53]

Symptoms without lactose challenge. Self reported history of LI related symptoms without empirical evidence of symptoms following a lactose challenge is very difficult to interpret. We identified seven studies reporting baseline self-reported symptoms representing 6,161 people.[29-34,35] Study characteristics from the identified studies are provided in Table 4. The population based nationally representative sample of U.S. adults by Nicklas and colleagues provides some evidence regarding the prevalence self-reported LI.[35] This study included 1,084 respondents 19 to 70 years of age, of which 486 were European American, 355 were African American, and 243 were Hispanic American. Data from this survey were combined with U.S. Census Bureau data to estimate an overall age adjusted prevalence of self reported LI of 12 percent. The specific racial/ethnic estimates were 8 percent for Caucasian adults, 20 percent for African American adults, and 10 percent for Hispanic Americans. This study did not attempt to validate the self reported results with either laboratory tests or clinician diagnoses.

Among non U.S. studies, one additional population based random sample of 1,978 Iranian adults showed a population self reported prevalence of 28 percent with no variation by age.[34] The generalizability of this one non U.S. study is difficult to put into a broader context without similar studies reporting different racial and ethnic populations and with greater variations in age.

Other than the one population based random sample in the United States, the rest of the self reported studies' results provide little evidence to address our research questions about population prevalence and the impact of age and ethnicity. Overall, the prevalence of self reported symptoms was typically lower than the prevalence of symptoms following a lactose challenge.

Lactose Malabsorption

Determined by hydrogen breath test following lactose challenge. Prevalence of LM, as diagnosed via a hydrogen breath test following a lactose challenge, has been frequently assessed in a wide range of studies from around the world. We identified 31 studies, including a total of nearly 12,000 participants from a wide range of ages and ethnicities.[7,8,10-12,14-17,20-25,28,30,32,36-42,44-48,156] The study characteristics from the identified studies are provided in Table 5. The studies in Table 5 are stratified into three different groups based on whether the participants self reported LI related symptoms prior to the challenge. Unfortunately, none of the U.S. studies were representative population based studies. In fact, all of the U.S. studies identified focused on reporting results in populations of patients with GI symptoms at baseline,[36,42,47,48] with the exception of one three decade old study of American Indians[30] and one convenience sample of adults from the Army, senior centers, nursing homes, and a university.[44]

Within the U.S. studies, the prevalence of LM in Caucasian adult populations ranged from 6 percent to 24 percent.[42,44,47] There were also some data suggesting high levels of LM among American Indians, but this effect was substantially attenuated among those with American Indian and Caucasian mixed ancestry.[30] Few data were eligible for this review for other racial and ethnic groups within U.S. populations, but a prior review of smaller and older studies using blood glucose tests suggested that the prevalence of LM may be greater than 70 percent in African Americans, around 50 percent in Hispanic Americans, and even higher for Asian

Americans.[49] Data for various racial and ethnic groups within the United States can likely be best understood by looking at the LM rates in the ancestral homelands of each of these ethnic groups.

The high prevalence of LM in the majority of non Northern European countries has been well known for decades. Earlier reviews captured many of the smaller and earlier studies, particularly those that used blood glucose tests.[49] The focus of this current review was more on LI as compared to LM. Similar to what has previously been reported, we found a wide range of LM rates that tended to be lowest among groups of Northern European ancestry, and relatively high in most other regions. Clearly, race and ethnicity have significant effects on the prevalence of LM; however, it is difficult to put precise estimates around the prevalence of LM for any group. In general, the majority of adults from populations with Northern European ancestry are able to digest lactose; whereas, the majority of adults who are Asian, African, American Indian, or from Sicily, Italy, (and actually much of the rest of the world) are unable to adequately digest 50 gram challenges of lactose. However, it is important to note that for many regions there is significant heterogeneity within the population in the ability of adults to digest lactose. This is particularly true within some regions in Africa,[37,38] but it has also been seen in other areas, such as in Italy.[11] However, much of the within country variation seen around the world is likely due to immigration that has occurred during the past couple of centuries.

Age is clearly an important contributor to the rate of LM, since nearly every population group identified, even those with high adult rates of LM, showed low rates of LM in the youngest age groups, particularly those less than 6 years of age.[16,17,23,28,39,45,46] In populations with high adult rates of LM, rates often seemed to nearly peak between 10 and 16 years of age.

Not unexpectedly, the dose of the lactose challenge appears to be an important factor in the reported prevalence of lactose malabsorption. Studies that included a lower dose challenge appeared to identify significantly fewer case of malabsorption.[12,16,23,41,46] Unfortunately, these lower dose studies were primarily only conducted in children, with the exception of a study of adults from Norway that found a 4 percent prevalence of LM following a 25 gram lactose challenge[12] and a study from Spain that found, compared to the standard challenge, a single serving of milk and a single serving of yogurt were much less frequently malabsorbed (33 percent, 14 percent, and 4 percent, respectively).[16]

Lactase Nonpersisters (Adult-type Hypolactasia Biopsy)

Biopsy identification. Five studies were identified that reported on the prevalence of lactase persistence as diagnosed by biopsy assays.[18,50-53] Generalizing results from these studies is more difficult since the studies were performed primarily in convenience samples of patients who had biopsy tissue available, often for clinical purposes, and these studies were all conducted decades ago (Table 6). The earliest study is the only study that provides estimates on lactase nonpersistence in a population of healthy U.S. Caucasians not thought to be intolerant to milk or to have GI symptoms.[53] This study, among adults with a mean age of 39 years, found 6 percent (6/100) had lactase activity $\leq$0.5 units per gram, and from these data the authors estimated that a population prevalence of hypolactasia would be between 1.3 percent to 10.3 percent (95 percent confidence level) for asymptomatic Caucasian adults.

One additional study from the United Kingdom provides a comparison of the prevalence of hypolactasia in four different groups of British adults who had biopsy jejunal tissue available: white subjects with normal histopathic biopsy, nonwhite subjects with normal histopathic biopsy, subjects with diarrhea following gastric surgery, and subjects with irritable bowel syndrome.[50]

There were no statistically significant differences in the frequencies of hypolactasia for white subjects (7/150; 5 percent), subjects with diarrhea following gastric surgery (3/36, 8 percent), or subjects with IBS (16/200, 8 percent); however, the prevalence of hypolactasia was substantially higher in the nonwhite subjects (15/29, 75 percent). The three remaining studies offer little data on the population prevalence of hypolactasia, since the study samples were highly selected for patients with clinical GI symptoms.[51-53] The first study found that both white children (ages 6 to 14) with recurrent abdominal pain and white children with chronic diarrhea had similar frequencies of hypolactasia—31 percent (8/26) and 36 percent (16/61), respectively.[51] Similarly, another study found children with IBS had a similar frequency (p-value=0.16) of hypolactasia (40 percent, 45/112) compared to children with chronic abdominal pain (30 percent, 34/112).[52] This study did report that within children with IBS, the nine black children had a significantly higher prevalence of hypolactasia compared to the 103 white children (78 percent versus 37 percent, respectively). The last study included a sample of 250 U.S. subjects with biopsy samples taken over a several year period with varied clinical reasons.[53] This study did have a sample with both age (2-81) and racial (white=209 and black=39) diversity; however, the hypolactasia results were not stratified by race. The overall prevalence of hypolactasia in the sample was 34 percent, but without race or age stratification it is difficult to generalize these findings to create any meaningful population estimates.

Genetic test association. Adult-type hypolactasia is thought to be an inherited autosomal recessive trait leading to decreased lactase activity in the intestinal mucosa. The most commonly reported genetic mutation for adult-type hypolactasia is the single nucleotide polymorphism (SNP) located 13,910 base pairs upstream of the lactase (LCT) gene of which the C allele is the globally most prevalent allele, while the less common T allele is associated with lactase persistence.[54]

Nine studies were identified that reported genotype frequencies for adult-type hypolactasia-linked LCT -13910C>T SNP mutation.[29,45,55-57,59-61,91] These studies included a total of 8,581 participants; however, none of these studies were of U.S. populations, and the majority of the people included in these studies had Northern European ancestry (Table 7). Not unexpectedly, there were no obvious differences in genotype by age group.[55,56] In North European studies, Caucasians had frequencies between 10-20 percent for the homozygous C/C genotype.[29,55-57,59,61] The frequency of the C/C genotype was somewhat higher in the one study from Austria (C/C=27 percent). Two studies reported results for the Italian regions of Sardinia[45,60] and Apulia[60] where the prevalence of the C/C genotype was between 80 percent and 90 percent. One study from Finland reported results in a subgroup of 65 children from Africa in which the prevalence of the C/C genotype was 95 percent.

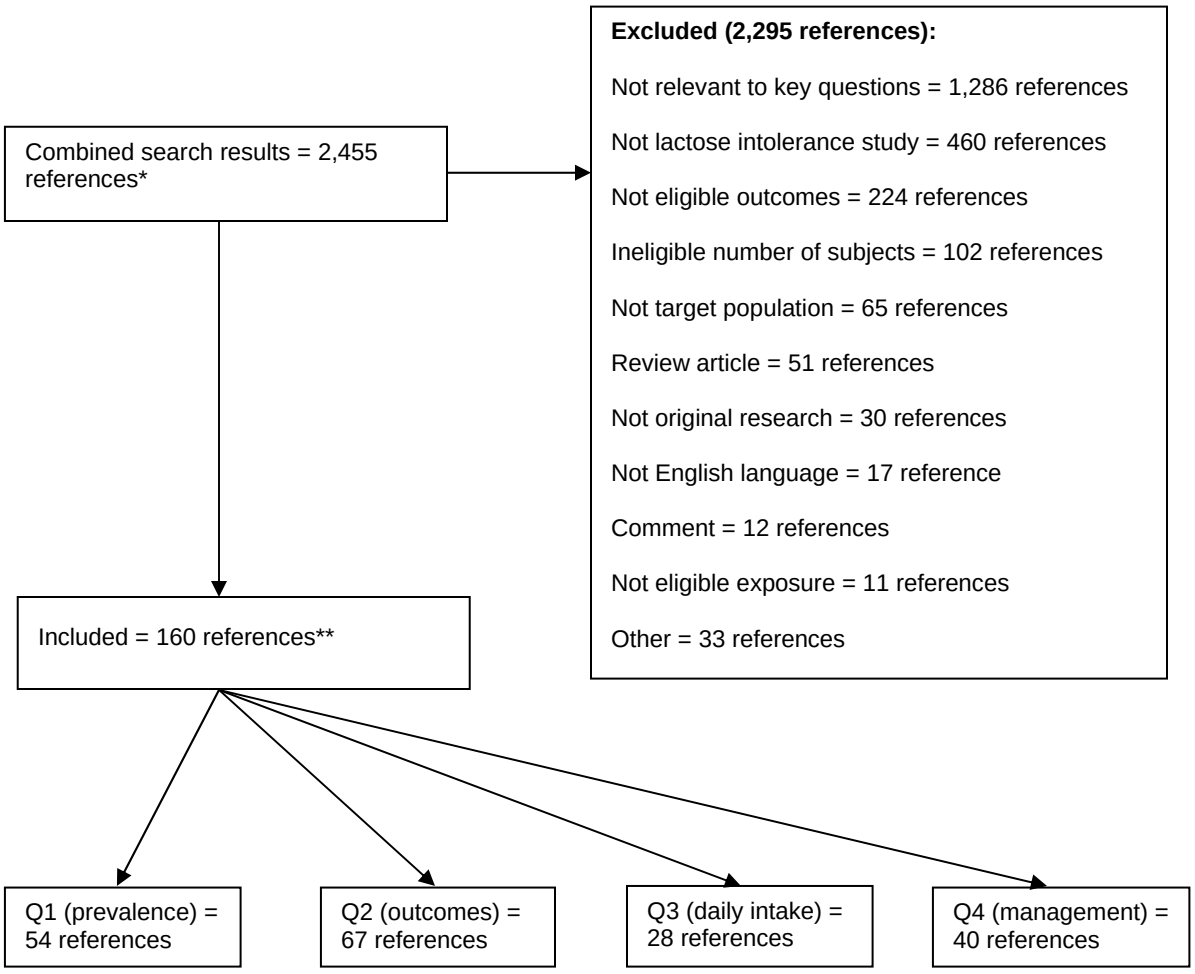
Results from genetic association tests consistently reported decreased consumption of milk (often on the order of twofold lower) in adults with the C/C genotype compared to those with at least one T allele.[56,57,59,61,91] These differences were smaller in healthy children.[59] The relative differences in calcium intake from all dairy and overall calcium intake were smaller than the differences in milk consumption.[29,57,59,91] All of these studies were from populations in Finland with generally high dairy consumption, except for one study in Austrian men where milk consumption was low in all men.[91]

Summary

There are few data available from recent U.S. studies regarding any of the outcomes we reviewed. The data that were available tended to be highly selected and not likely representative of the overall U.S. population. Finally, the outcomes that have been reported do not directly assess LI, but instead assess either an inability to fully absorb lactose or somewhat subjective symptoms that are prone to biased reporting. This lack of data may in part be due to the fact that LI is a difficult condition to define. The lack of a clear, clinically meaningful, and commonly accepted definition of LI may partly explain the limited information available for characterizing the U.S. population prevalence.

While precise estimates of the U.S. prevalence of LI are not possible, there is evidence that the magnitude of LI will be very low in young children and likely remain low into adulthood for most populations of Northern European decent. For African American, Hispanic, Asian, and American Indian populations the rates of LI will likely be higher in late childhood and adulthood; however, smaller doses of lactose might be generally well tolerated in most populations.

Figure 2. Reference flow diagram



* Searches of PubMed®, MEDLINE® (OVID), and the Cochrane Central Register of Controlled Trials (CENTRAL) were combined and duplicate listings were removed.

** The total number of included references is not a sum of eligible references for each question because of overlapping eligibility.

Table 3. Prevalence of lactose intolerance symptoms following challenge

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Asymptomatic at baseline				
Ahmad, 1984[7] Pakistan (N. Panjab)	N=414 Subject selection: healthy, well-nourished Pakistani adults Inclusion/exclusion: NA	Mean age: 28.3 (range 18-48) Males: n=404 Females: n=10 Race/ethnicity: Panjabi	Challenge: 50 g lactose/400 ml water Symptoms (gas and/or diarrhea)	Overall: NA Subgroup In malabsorbers: 122/216 (56.5%)
Bolin, 1970[157] Australia	N=100 Subject selection: healthy adults Inclusion/exclusion: NA	Mean age: NA (18-40) Males: n=62 Females: n=38 Race/ethnicity: Australians	Challenge: 50 g lactose/400 ml water Symptoms (abdominal pain, diarrhea)	Overall: 6/100 (6%) Subgroups Males: 0/62 (0%) Females: 6/38 (15.8%)
Bujanover, 1985[10] Israel	N=110 Subject selection: healthy subjects Inclusion/exclusion: All were antibiotic and drug free 1 month prior to entrance; all were consuming dairy products.	Mean age: 6 years 7 months (4 months-15 years) Males: n=61 Females: n=49 Race/ethnicity: Israeli Jews	Challenge: 2 g/kg lactose up to 50 g (10% solution) Symptoms: abdominal pain, diarrhea or soft stool with increased number of bowel movements, nausea and vomiting, flatulence, borborygmi	Overall: NA Subgroups In malabsorbers: 41/68 (60.3%) By age **Years** / **n/N (%)** 0-3: 0/12 (0) 3-6: 6/23 (26.1) 6-12: 18/46 (39.1) 12-16: 16/29 (55)
Burgio, 1984[11] Italy	N=308 Subject selection: healthy Italian adults Inclusion/exclusion: NA	Mean age: 43.2 Males: n=116 Females: n=192 Race/ethnicity: Italians of Sicilian, N. Italian descent	Challenge: 50 g lactose/400 ml of boiled tap water Symptoms: abdominal distention, colics, borborygmi, flatulence	Overall: 71/308 (23%) Subgroups Milk intolerance in malabsorbers: 51/177 (29%) Milk intolerance in absorbers: 20/131 (15%)
Ladas, 1991[15] Greece	N=150 (baseline symptoms n=43) Subject selection: Greek children selected by their teacher-assigned number Exclusion: One child was excluded because of a known milk allergy (atopic dermatitis).	Mean age: NA (5-12) Males: n=72 Females: n=78 Race/ethnicity: Greeks	Challenge: 2 g lactose/kg to a maximum of 50 g and 0.240 L of milk (12 g lactose) Symptoms: colicky pain, abdominal distention with flatulence and diarrhea, as well as the frequency and consistency of bowel movements	2 g lactose/kg to a maximum of 50 g In absorbers: 29.6% In malabsorbers:50.7% P = 0.008 0.240 L of milk (12 g lactose) In absorbers: 6/81 (7.3%) In malabsorbers: 6/69 (8.6%) P = 0.72 Age 5: 5/17 (29.4%) Age 12: 8/10 (80%)

Table 3. Prevalence of lactose intolerance symptoms following challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Leis, 1997[16] Spain	N=850 Subject selection: healthy subjects from Galicia Spain with no history of GI illness Inclusion/exclusion: 1) not eaten or drunk anything for at least 12 hours; 2) not smoked for at least 6 hours (and did not smoke during the test); 3) not slept or done heavy physical exercise for at least 1 hour; 4) cooperated readily in the test, without hyperventilation or crying; 5) no antibiotics or laxatives for at least 15 days, and had not used any other drug on the day of the test; and 6) had gotten a positive breath hydrogen test after ingestion of 1 g/kg body weight of lactulose, so the enteric bacterial flora was able to produce hydrogen	Mean age: NA Males: n=397 Females: 453 Race/ethnicity: Galician Spaniards	Challenge: 2 g lactose/kg up to 50 g 250 ml of milk 250 ml of yogurt Symptoms (vomiting, nausea, diarrhea, belching, flatulence, abdominal pain, distension)	Overall: NA Subgroups In malabsorbers (2 g lactose/kg): 150/276 (54.3%) Ages 3-5: 0/9 (0%) (2 g lactose/kg) Ages 6-13: 33/76 (43.4%) Ages 14-18: 36/76 (47.4%) Ages 19-24: 34/47 (72.3%) Ages 25-60: 41/53 (77.4%) Age >60: 6/15 (40%) In malabsorbers (250 ml of milk): 5/27 (18.5%) Ages 3-5: 0/0 (0%) (250 ml of milk) Ages 6-13: 1/6 (16.7%) Ages 14-18: 1/11 (9.1%) Ages 19-24: 2/4 (50%) Ages 25-60: 0/0 (0%) Age >60: 1/6 (16.7%)
Newcomer, 1967[18] USA	N=100 Subject selection: healthy Caucasian volunteers Inclusion: no history of milk intolerance	Mean age: 38.5 (20-63) Males: 37 (20-63) Females: 40 (21-62) Males: n=50 Females: n=50 Race/ethnicity: Caucasian	Challenge: 50 g lactose/500 ml water Symptoms: diarrhea, cramping, bloating, borborygmi, flatulence	Overall: NA Subgroups In malabsorbers: 6/6 (100%) In absorbers: 2/57 (3.5%)
Rosado, 1994[19] Mexico	N=926 Subject selection: randomly selected subjects from 3 regions Inclusion/exclusion: healthy, taken no meds, antibiotics for last 3 weeks, <60 years old	Mean age: 14.9 N. Mexico: 14.1 C. Mexico: 15.8 S. Mexico: 14.3 Males: NA Females: NA Race/ethnicity: Mayan, “mixed”	Challenge: 240 or 360 ml of whole intact cow's milk (12 or 18 g of lactose, respectively) Symptoms: headache, gas, flatulence, abdominal cramps, leg pain, diarrhea	Overall: 151/926 (16.3%) Subgroups: Age Years — n/N (%) <4 — 8/115 (7) 4 to <8 — 23/239 (9.6) 8 to <13 — 38/227 (16.7) Adult — 82/345 (23.8)

Table 3. Prevalence of lactose intolerance symptoms following challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Segal, 1983[21] South Africa	N=115 Subject selection: healthy adult volunteers Exclusion: GI symptoms	Mean age: 32.5 Males: NA Females: NA Race/ethnicity: Zulu, Xhosa, Sotho, Tswana, Swazi, Shangaan	Challenge: 50 g lactose/400 ml water Symptoms: abdominal discomfort, borborygmi, diarrhea	Overall: 32/115 (30%)
Ting, 1988[23] Republic of China (Taiwan)	N=726 Subject selection: subjects in good health, without diarrhea or antibiotic therapy for at least 1 week prior to study Inclusion/exclusion: NA	Mean age: NA (3-18) Males: NA Females: NA Race/ethnicity: Chinese	Challenge: 0.5 g lactose/kg Symptoms: abdominal pain, diarrhea, and/or flatulence	Overall: NA Subgroups Age (years) n/N (%) 3 0/8 (0) 4 0/33 (0) 5 0/63 (0) 6 0/109 (0) 7 -- 9, 10 3/67 (4.5) 8 0/56 (0) 11, 12 17/79 (21.5) 13, 14 22/69 (31.9) 15, 16 17/62 (27.4) 17, 18 16/52 (30.8)
Wang, 1984[25] China	N=641 Subject selection: healthy, well-nourished, volunteers Inclusion/exclusion: NA	Mean age: 22.9 (16-46) Males: n=447 Females: n=194 Race/ethnicity: Han, Mongols, and Kazakhs from N. China	Challenge: 50 g lactose Symptoms: gas and/or diarrhea	Overall: 287/641 (45%) Subgroups Absorbers: 13/89 (14.6%) Malabsorbers: 274/552 (50%)
Yang, 2000[28] China	N=1168 Subject selection: Healthy subjects recruited from schools in large cities. Inclusion/exclusion: diarrhea, chronic constipation or other GI problems, no use of any drugs 1 week prior to test, good general health without signs of acute or chronic illness	Overall mean age: 8.0 (3-13) Males: n=610 Females: n=558 Race/ethnicity: Chinese	Challenge: 25 g lactose or 50 g milk Symptoms: bloating, pain, diarrhea	Overall: 296/1168 (25.3%) Subgroups: Age Years n/N (%) 3-5 47/387 (12.2) 7, 8 132/399 (33.1) 11-13 117/382 (30.5)

Table 3. Prevalence of lactose intolerance symptoms following challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Symptomatic at baseline				
Beyerlein, 2008[8] Switzerland	N=1,127 Subject selection: data from all patients referred for H_2-BT between 1999 and 2005 were collected prospectively Inclusion/exclusion: patients were asked to fast and refrain from smoking for at least 6 hours prior to the test. Patients were also asked to discontinue use of antibiotics 1 week and laxatives 1 day before the hydrogen breath test	Mean age: 39.8 (7-87) Males: n=320 Females: n=807 Race/ethnicity: "Swiss," "non-Swiss"	Challenge: 50 g lactose Symptoms: nausea, abdominal pain, borborygmi, bloating and diarrhea	Overall: 326/1127 (28.9%) Subgroup: Swiss: 241/746 (32.3%) Non-Swiss: 85/381 (22.3%)
Hermans, 1997[14] The Netherlands	N=309 Subject selection: Consecutive adult patients with suspected LM underwent a lactose tolerance test. Exclusion: Subjects who were treated with antibiotic drugs or underwent bowel preparation for an endoscopic or a radiological investigation within 4 weeks before the test, as well as those with diabetes mellitus, were excluded from the study.	Mean age: 42 Males: n=130 Females: n=179 Race/ethnicity: NA	Challenge: 50 g lactose Symptoms: Total symptom score was 0-8, with 8 being most severe. Each symptom (bloating, flatulence, abdominal distension, diarrhea) was scored with 0 (no complaints), 1 (moderate), 2 (severe), with diarrhea always scored as a 2.	Overall: 220/309 (71.2%) Subgroups Total symptom score (0-8) / n/N (%) 0: 89/309 (28.8) 1: 115/309 (37) 2: 84/309 (27) 3: 23/309 (7.4) 4: 7/309 (2.3)
Symptomatic and asymptomatic at baseline				
Farup, 2004[12] Norway	N=187 (Irritable bowel syndrome Group n=82, Controls n=105) Subject selection: A population-based, case-controlled, health study. Persons with irritable bowel syndrome (Rome II criteria) and alarm symptoms were invited to follow up. Also invited was a group of healthy Norwegians to participate in the study as a control group. Exclusion: organic disease	Mean age: 47 Males: n=49 Females: n=138 Race/ethnicity: Norwegians	Challenge: 25 g lactose Symptoms: abdominal pain/discomfort, borborygmi, bloating, diarrhea, or constipation	Overall: N/A Subgroups Irritable bowel group: 28/74 (38%) Controls: 21/104 (20%) P=0.011 Total symptom score after challenge Irritable bowel group (n=82): 3.5 Controls (n=105): 1.7 P=0.011

Table 3. Prevalence of lactose intolerance symptoms following challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Garza, 1976[13] USA	N=99 Sample: healthy White and Black children Inclusion/exclusion: NA	Mean age: NA (4-9) Males: NA Females: NA Race/ethnicity White: n=30 Black: n=69	Challenge: 2 g lactose/kg to a maximum of 50 g Symptoms	Overall: NA Subgroups Age / N / % (95% CI) Blacks 4,5 / 9 / 11 (0-46) 6,7 / 24 / 50 (27-71) 8,9 / 29 / 72 (51-86) Whites 4,5 / 2 / 0 (0-0) 6,7 / 14 / 0 (0-23) 8,9 / 10 / 20 (2-57)
Maggi, 1987[17] Uruguay	N=200 Subject selection: randomly selected volunteer subjects were prospectively studied Inclusion/exclusion: NA	Mean age: NA (0-86) Males: n=100 Females: n=100 Race/ethnicity Whites: n=184 Blacks: n=16	Challenge: 2 g lactose/kg body weight or 50 g lactose/m^2 body surface Symptoms	Overall: 65/200 (32.5%) Subgroups In LM in subjects >20 years old: 31/78 (40%)
Seakins, 1987[20] Samoa, New Zealand, Cook Islands	N=207 Subject selection: Samoan children were studied in four locations, two in W. Samoa and two in New Zealand. White children were studied in the Cook Islands and New Zealand. Inclusion/exclusion: NA	Mean age: NA (6-13) Males: n=NA Females: n=NA Race/ethnicity Somoans: n=139 Whites: n=68	Challenge: 10 g lactose/100 ml orange flavored, carbohydrate-free cordial Symptoms from milk (abdominal bloating and pain, flatulence, and diarrhea)	Overall: 24/207 (11.6%) Subgroups Samoans: 16/139 (11.5%) Whites: 8/68 (11.8%)
Socha, 1984[22] Poland	N=275 (historical milk intolerance, n=15) Subject selection: healthy Polish adolescents and adults Inclusion/exclusion: NA	Mean age: 29.1 (16-59) Males: n=61 Females: n=214 Race/ethnicity: NA	Challenge: 50 g lactose/400 ml water Symptoms: abdominal pain and distension, flatulence, borborygmi, nausea, diarrhea	Overall: 110/263 (41.8%) Subgroups In malabsorbers: 69/100 (69%) In absorbers: 41/163 (25%) In historical milk intolerants: 39/44 (88.6%) In historical milk tolerants: 71/219 (32.4%)

Table 3. Prevalence of lactose intolerance symptoms following challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Intolerance Symptoms
Vernia 2004[24] Italy	N=402 Subject selection: consecutive IBS patients diagnosed by Rome criteria Inclusion/exclusion: NA	Mean age: 35.1 Males: n=120 Females: n=282 Race/ethnicity: NA	Challenge: 0.5 g lactose/kg up to a maximum of 25 g Symptoms	Overall (self reported symptoms and + breath test): 290/402 (72%) Subgroups Symptoms and + breath test in milk consumers: 138/201 (68.6%) Symptoms and + breath test in alleged milk intolerant patients: 152/201 (75.6%)
Woteki, 1976[27] USA	N=339 Subject selection: normal and healthy as described by school nurse Exclusion: known GI diseases, or diabetes; secondary lactase deficiency	Mean age: 7.5 (2-14) Males: "approximately equal numbers" Females: "approximately equal numbers" Race/ethnicity Mexican American: n=282 Anglo American: n=51	Challenge: 2 g lactose/kg up to a maximum of 50 g Symptoms	Overall: 126/333 (37.8%) Subgroups Mexican Americans: 116/282 (41%) Anglo Americans: 10/51 (20%) P <0.005

Age group	Mean age	n/N (%)
Mexican Americans		
2-5	4.0	16/88 (18)
6-9	7.8	50/119 (42)
10-14	11.0	50/75 (67%)
Total	7.5	116/282 (41%)
Anglo Americans		
2-5	4.7	0/3 (0)
6-9	7.9	5/31 (16)
10-14	10.4	5/17 (29)
Total	8.6	10/51 (20)

Woteki,1977[26] USA	N=419 Subject selection: volunteers were solicited from within the San Antonio area Exclusion: diabetes, digestive or liver diseases, previous GI surgery (excepting appendectomy)	Mean age: 32.6 (18-94) Males: NA Females: NA Race/ethnicity Mexican-American: n=277 Anglo American: n=142	Challenge: 50 g lactose Symptoms	Overall: 253/419 (60.4%) Subgroups Mexican-Americans: 186/277 (67%) Anglo Americans: 67/142 (47%)

Table 4. Prevalence of lactose intolerance by self report

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Lactose Intolerance
Symptomatic and asymptomatic at baseline				
Ennattah, 2005[29] Finland	N=564 Subject selection: cross-sectional, cohort study of population-based, postmenopausal women (n=453), women with osteoporotic fractures (n=52), and a control group of women without osteoporosis (n=59) Inclusion/exclusion: NA	Mean age: 70 (62-85) Mean age (population-based cohort): 69 (62-78) Males: n=0 Females: n=564 Race/ethnicity: Finns	Self report	Overall (population-based cohort): 72/451 (16%)
Johnson, 1978[30] USA	N=109 Sample: Native Americans with full and mixed blood from various tribes from the American Great Basin and South West Excluded: subjects with diabetes or a recent history of diarrhea or intestinal surgery	Mean age: >18 years Males: NA Females: NA Race/ethnicity: Native Americans	Self report	Overall: 30/109 (27.5%)
Johnson 1980[31] USA (Hawaii), Republic of China (Taiwan), Japan, Republic of Korea (S. Korea), Peoples' Republic of China	N=1,452 Subject selection: Questionnaire administered to students in the U.S., Taiwan, and Japan Inclusion/exclusion: NA	Mean age: NA Males: NA Females: NA Race/ethnicity: Hawaii subjects Caucasians: n=177 Chinese: n=58 Filipino: n=49 Hapa-Haole (either ½ Chinese, Japanese or Korean & ½ European): n=22 Hawaiian (or partial): n=52 Japanese: n=366 Homeland Chinese: n=296	Self report	Overall: NA Subgroups Retrospective childhood symptoms in populations that consume little or no milk at present Stomach problems / Diarrhea National/ethnic group: n/N (%) Hawaiian Caucasian: 29/177 (16.4) / 20/177 (11.3) Asian/Pacific Rim†: 165/547 (30.2) / 162/547 (29.6) Foreign Asian*: 290/728 (39.8) / 280/728 (38.5) *Chinese (N=296), Japanese (N=192), and

Table 4. Prevalence of lactose intolerance by self report (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Lactose Intolerance
		Homeland Japanese: n=192 Homeland Koreans: n=240		Korean (N=240). †Hawaiian Chinese (N=58), Filipino (N=49), Hapa-Haole (N=22), Hawaiian or partial (N=52). Self-reported symptoms from milk drinking from populations that consume little or no milk at present **Stomach Problems** / **Diarrhea** National/Ethnic Group: n/N (%) Hawaiian Caucasian: 22/177 (12.4) / 9/177 (5.1) Asian/Pacific Rim†: 182/547 (33.3) / 107/547 (19.6) Foreign Asian*: 141/728 (19.4) / 158/728 (21.7) *Chinese (N=296), Japanese (N=192), and Korean (N=240). †Hawaiian Chinese (N=58), Filipino (N=49), Hapa-Haole (N=22), Hawaiian or partial (N=52)
Kokkonen 2001[32] Finland	N=260 Subject selection: Fifty-six 10-year-old subjects (n=56) who manifested cow's milk allergy before 1 year of age, compared to a group (n=204) randomly selected age-matched school children. Children underwent a blind, placebo-controlled milk challenge. Inclusion: children with abdominal pain or reported complaints compatible with lactose intolerance (e.g., flatulence, diarrhea, abdominal pain)	Mean age (subjects with cow's milk allergy): 10.5 (9-11) Males: n=35 Females: n=21 Race/ethnicity: Finns	Self report	Overall Cow's milk allergy Group: 17/56 (30%) Controls: 18/204 (9%) P < 0.0001

Table 4. Prevalence of lactose intolerance by self report (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Lactose Intolerance
Nicklas, 2009[35] USA	N=1,084 Subject selection: participants were selected from a representative sample of randomly generated telephone numbers from a commercial provider Inclusion: NA	Mean age: NA Males: n=351 Females: n=733 Race/ethnicity European Americans: n=486 African Americans: n=355 Hispanic Americans: n=243	Self report	Overall (age adjusted): 12.04% Subgroups (age adjusted) European Americans: 7.72% African Americans: 19.50% Hispanic Americans: 10.05% European American males: 7.39% European American females: 7.91% African American males: 15.42% African American females: 20.81% Hispanic American males: 8.42% Hispanic American females: 10.57%
Paajanen 2005[33] Finland	N=827 (Controls n=29) Subject selection: Study group was drawn from a population-based cohort of children living in northern Finland, who were initially recruited in 1994 for a study of risk factors for Type 1 diabetes. Inclusion/exclusion: celiac disease, A–class antibodies to tissue transglutaminase, Type I diabetes	Mean age: NA (16-21) (from original cohort of 3,652) Males: n=367 Females: n=460 Race/ethnicity: Finns	Self report	Overall (self-diagnosed + physician diagnosed LI): 108/827 (13.1%, 95% CI 10.8%-15.4%)
Saberi-Firoozi 2007[34] Iran	N=1978 Subject selection: healthy cohort in Shiraz, Iran, chosen by cluster randomization Inclusion/exclusion: NA	Mean age: 49.9 Males: n=709 Females: n=1,269 Race/ethnicity: Iranians	Self report (questionnaire—subjective symptoms by Rome II criteria)	Overall LI: 562/1978 (28.4%) Subgroups Gender: n/N (%) Female: 178/709 (25.1)* Male: 384/1269 (30.3) Age groups 35-44: 219/734 (29.8) 45-54: 191/646 (29.6) 55-64: 85/343 (24.8) 65-74: 53/200 (26.5) ≥ 75: 13/53 (24.5) *P=0.015

Table 5. Prevalence of lactose malabsorption by challenge

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
Asymptomatic at baseline				
Ahmad, 1984[7] Pakistan (N. Panjab)	N=414 Subject selection: healthy, well-nourished Pakistani adults Inclusion/exclusion: NA	Mean age: 28.3 (18-48) Males: n=404 Females: n=10 Race/ethnicity: Panjabi	Challenge: 50 g lactose/400 ml water Hydrogen breath test	Overall: 216/414 (52%)
Bayoumi, 1981[38] Sudan	N=563 Subject selection: healthy Sudanese adults Inclusion/exclusion: NA	Mean age: NA Males: n=549 Females: n=14 Race/ethnicity: Sudanese	Challenge: 50 g lactose/400 ml water Hydrogen breath test	Overall: 310/563 (55.1%)
Bayoumi, 1982[37] Sudan	N=585 Subject selection: healthy, well nourished adults Inclusion/exclusion: NA	Mean age: 21.4 (14-50) Males: 483 Females: n=102 Race/ethnicity: NE. and S. Sudanese	Challenge: NA Hydrogen breath test	Overall: 261/585 (45%) Subgroups **Age group (years) / n/N (%)** 14-18: 95/219 (43.4) 19-30: 137/295 (46.4) 30+: 29/68 (42.6)
Beyerlein, 2008[8] Switzerland	N=1127 Subject selection: Data from all patients referred for hydrogen breath test were collected prospectively. Inclusion/exclusion: Patients were asked to fast and refrain from smoking for at least 6 hours prior to the test. Furthermore, patients were asked to discontinue use of antibiotics 1 week and laxatives 1 day before the hydrogen breath test.	Mean age: 39.8 (7-87) Males: n=320 Females: n=807 Race/ethnicity: “Swiss,” “non-Swiss”	Challenge: 50 g of lactose dissolved in 300 ml of water Hydrogen breath test	Overall: 376/1127 (33%) Subgroup Swiss: 23%, Non-Swiss: 54%

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
Bujanover, 1985[10] Israel	N=110 Subject selection: healthy subjects Inclusion/exclusion: All were antibiotic and drug free 1 month prior to entrance; all were consuming dairy products.	Mean age: 6 years 7 months (4 months-15 years) Males: n=61 Females: n=49 Race/ethnicity: Israeli Jews	Challenge: 2 g/kg lactose up to 50 g (10% solution) Hydrogen breath test	Overall: 68/110 (61.6%) Subgroups And symptoms: 41/68 (60.3%) Age Years n/N (%) 0-3 0/12 (0) 3-6 13/23 (56.5) 6-12 30/46 (65.2) 12-16 22/29 (75)
Burgio, 1984[11] Italy	N=308 Subject selection: healthy Italian adults Inclusion/exclusion: NA	Mean age: 43.2 Males: n=116 Females: n=192 Race/ethnicity: Italians of Sicilian, N. Italian descent	Challenge: 50 g lactose/400 ml water Hydrogen breath test	Overall: 177/208 (85%) Subgroups N. Italy: 106/208 (51%) Sicily: 71/100 (71%)
Czeizel, 1983[40] Hungary	N=820 Subject selection: healthy adult and adolescent Hungarian subjects Inclusion/exclusion: NA	Mean age: 26.2 (16-54) Males: n=260 Females: n=560 Race/ethnicity: Magyars (n=535), Matyo (n=172), and Romai (n=113)	Challenge: 50 g lactose Hydrogen breath test	Overall: 323/820 (39%) Subgroups Magyars: 198/535 (37%) Matyos: 63/172 (36.6%) Romai: 63/113 (56%)
Debrot, 1990[41] Curaçao, Netherlands Antilles	N=729 Subject selection: children aged 8-10 years who attended elementary schools in Curaçao Inclusion/exclusion: NA	Mean age: 8.9 (8-10) Males: NA Females: NA Race/ethnicity: “Blacks”	Challenge: 0.5 g lactose/kg body weight Hydrogen breath test (n=692)	Overall: 97/692 (14%)
Leis, 1997[16] Spain	N=850 Subject selection: healthy subjects from Galicia Spain with no history of GI illness Inclusion/exclusion: 1) not eaten or drunk anything for at least 12 hours; 2) not smoked for at least 6 hours (& did not smoke during the test); 3) not slept or done heavy physical exercise for at least 1 hour; 4) cooperated	Mean age: NA Males: n=397 Females: 453 Race/ethnicity: Galician Spaniards	Challenge: (1) 2 g lactose/kg up to 50 g (2) 250 ml of milk, (3) 250 ml of yogurt Hydrogen breath test	Overall (2 g lactose/kg): 276/850 (32.5%) Overall (250 ml milk): 116/850 (13.7%) Overall (250 ml yogurt): 32/850 (3.8%) Subgroups (2 g lactose/kg) In symptomatics: 150/276 (54.3%) In asymptomatics: 126/276 (45.7%) Ages 3-5: 9/95 (9.5%) (2 g lactose/kg) Ages 6-13: 76/209 (36.4%) Ages 14-18: 76/208 (36.5%) Ages 19-24: 47/138 (34.1%) Ages 25-60: 53/137 (38.7%)

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
	readily in the test, without hyperventilation or crying; 5) had not taken antibiotics or laxatives for at least 15 days, and had not used any other drug on the day of the test; and 6) had gotten a positive breath hydrogen test after ingestion of 1 g/kg body weight of lactulose, so the enteric bacterial flora was able to produce hydrogen			Age >60: 15/63 (23.8%) Ages 3-5: 0/8 (0%) (250 ml of milk) Ages 6-13: 6/73 (8.2%) Ages 14-18: 11/56 (19.6%) Ages 19-24: 4/16 (25%) Ages 25-60: 0/30 (0%) Age >60: 6/14 (42.9%)
Segal, 1983[21] South Africa	N=115 Subject selection: healthy adult volunteers Exclusion: GI symptoms	Mean age: 32.5 Males: NA Females: NA Race/ethnicity: Zulu, Xhosa, Sotho, Tswana, Swazi, Shangaan	Challenge: 50 g cow's milk/400 ml water Hydrogen breath test	Overall: 90/115 (78.3%)
Tadesse, 1991[46] Hong Kong	N=320 (outcomes were for 276; 44 were noncompliant) Subject selection: Subjects from primary and secondary school were invited to participate. Exclusion: GI complaints, no antibiotic treatment for last month before entry	Median age: 11.4 (6.5-18.3) Males: n=134 Females: n=142 Race/ethnicity: Chinese	Challenge: 5 ml cow's milk/kg body weight (~0.25g lactose/kg body weight) Hydrogen breath test	Overall: 35/276 (12.7%) Subgroups Age **Years** / **n/N (%)** / **95% CI** 6, 7 — 0/23 (0) — 0-14.8 8, 9 — 3/66 (4.6) — 1.0-12.7 10, 11 — 3/56 (5.4) — 1.1-14.9 12, 13 — 3/35 (8.6) — 1.8-23.1 14, 15 — 15/66 (22.7) — 13.3-34.7 16-18 — 11/30 (36.7) — 19.9-56.1 Total — 35/276 (12.7) — --
Ting, 1988[23] Republic of China (Taiwan)	N=726 Subject selection: subjects in good health, without diarrhea or antibiotic therapy for at least 1 week prior to study Inclusion/exclusion: NA	Mean age: NA (3-18) Males: NA Females: NA Race/ethnicity: Chinese	Challenge: 0.5 ml lactose/kg body weight Hydrogen breath test	Overall: NA Age **Years** / **n/N** / **%** / **Chi^2** 3 — 0/8 — 0.0 — -- 4 — 4/33 — 12.1 — NS 5 — 9/63 — 14.3 — NS 6 — 13/109 — 12.1 — p<0.001 7 — 55/128 — 43.0 — -- 8 — 27/56 — 48.2 — NS 9, 10 — 40/67 — 59.7 — NS 11, 12 — 51/79 — 64.6 — NS

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
				13, 14 51/69 73.9 NS 15, 16 42/62 68.5 NS 17, 18 37/52 71.2 NS
Wang, 1984[25] China	N=641 Subject selection: healthy, well-nourished, volunteers Inclusion/exclusion: NA	Mean age: 22.9 (16-46) Males: n=447 Females: n=194 Race/ethnicity: Han, Mongols, and Kazakhs from N. China	Challenge: 50 g lactose Symptoms: gas and/or diarrhea	Overall: 552/641 (86%) Subgroups Han: 229/248(92.3%) Mongols: 174/198 (87.9%) Kazakhs: 149/195 (76.4%)
Yang, 2000[28] China	N=1168 Subject selection: healthy subjects recruited from schools in large cities. Inclusion/exclusion: diarrhea, chronic constipation or other GI problems, no use of any drugs 1 week prior to test, good general health without signs of acute or chronic illness	Overall mean age: NA (3-13) Males: n=610 Females: n=558 Race/ethnicity: Chinese	Challenge: 50 g lactose Hydrogen breath test	Overall: 835/1168 (71.4%) Subgroup: Age Years n/N (%) 3-5 150/387 (38.7) 7, 8 350/399 (87.8) 11-13 335/382 (87.8)
Symptomatic at baseline				
Barr, 1979[36] USA	N=80 Subject selection: children seen at a general medicine clinic during a 12-month period Inclusion: symptomatic for a primary complaint of intermittent abdominal pain of unexplained origin, more than 3 episodes of pain in <3 months, and of sufficient severity to affect activity Excluded: children with transient GI dysfunction	Mean age: 9.6 (4-15) Males: NA Females: NA Race/ethnicity White: n=59 Black: n=16 Hispanic: n=5	Challenge: 2 g lactose/kg up to 50 g Hydrogen breath test	Overall: 32/80 (40%) Subgroups White: 16/59 (27%) Black: 12/16 (75%) Hispanic: 4/5 (80%)
Hermans, 1997[14] The Netherlands	N=309 Subject selection: Consecutive adult patients with suspected LM underwent a lactose tolerance test.	Mean age: 42 Males: n=130 Females: n=179 Race/ethnicity: NA	Challenge: 50 g lactose Hydrogen breath test	Overall: 122/309 (39.5%)

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
	Exclusion: Subjects who were treated with antibiotic drugs or underwent bowel preparation for an endoscopic or a radiological investigation within 4 weeks before the test as well as those with diabetes mellitus were excluded from the study.			
Kokkonen, 2001[32] Finland	N=260 Subject selection: 10-year-old subjects with cow's milk allergy before 1 year of age, and compared to a group of 204 randomly selected age-matched school children Inclusion: children who had abdominal pain or reported complaints compatible with lactose intolerance (e.g., flatulence, diarrhea, abdominal pain)	Mean age: 10.5 (9-11) Males: n=35 Females: n=21 Race/ethnicity: Finns	Challenge: 2 g lactose/kg in 250 ml water Hydrogen breath test	Overall Study group: 8/56 (14%) Controls: 6/204 (3%) P <0.001
Montes, 1993[156] USA	N=494 Subject selection: (Group 1) children of diverse ethnic backgrounds from Maryland or Pennsylvania (n=385); also reviewed were the lactose hydrogen breath test results of 109 lactose-malabsorbing patients (Group 2) tested at home or in a physician's office. Eighty-nine of these subjects were children (81.6%). Inclusion: GI complaints, such as diarrhea and abdominal pain	Group 1 (n=385) Mean age: NA (2.5-21) Males: NA Females: NA Group 2 (n=109) Mean age: 8.6 (1-16) Adults: n=20 (Mean age 43.2) Children: n=89 Race/ethnicity: NA	Challenge: 2 g lactose/kg up to 50 g Hydrogen breath test	Overall: 252/494 (51%) Subgroup Group 1: 70/385 (18%)
Newcomer, 1983[42] USA	N=80 Subject selection: healthy Caucasian volunteers with no	Overall mean age: 50.3 (26-82) Males: n=16 Females: n=64	Challenge: 50 g lactose/500 ml water Hydrogen breath test	Overall: 5/80 (6%)

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
	history of intolerance to milk Inclusion: irritable bowel syndrome	Race/ethnicity: "White, non-Jewish, NW European background"		
Tolliver, 1994[47] USA	N=196 Subject selection: Subjects who met the International Congress of Gastroenterology criteria for IBS were prospectively sampled by hematological, biochemical and metabolic lab testing, as well as evaluation of colon. Inclusion: Patients had to meet the International Congress of Gastroenterology criteria for Irritable Bowel Syndrome.	Mean age: 43.7 (18-76) Males: n=38 (19%) Females: n=158 (81%) Race/ethnicity: NA	Challenge: 50 g lactose/200 ml water Hydrogen breath test	Overall: 48/196 (24%)
Vernia, 2003[24] Italy	N=402 Subject selection: consecutive IBS patients diagnosed by Rome criteria Inclusion/exclusion: NA	Mean age: 35.1 Males: n=120 Females: n=282 Race/ethnicity: NA	Self report	Overall: 290/402 (72%) Subgroups Self-reported milk consumers: 138/201 (68.6%) Self-reported milk intolerant patients: 152/201 (75.6%)
Webster, 1995[48] US	N=137 Subject selection: Subjects were referred for specialty evaluation of recurrent abdominal pain of at least 3 months' duration. Inclusion/exclusion: NA	Mean age: 9.6 (6-18) Males: n=53 Females: n=84 Race/ethnicity: Caucasians (n=114) and African Americans (n=23)	Challenge: 1 g lactose/kg lactose 10% aqueous solution) up to 50 g Hydrogen breath test	Overall: 33/137 (24%) Subgroups African Americans: 10/23 (43%) Caucasians: 23/114 (20%) P <0.02
Symptomatic and asymptomatic at baseline				
Carroccio, 1998[39] Italy	N=323 (historical self-reported tolerants (n=274) and intolerants (n=49) Subject selection: a randomized sample of the general population in a small center in Sicily; subjects were then divided into self-reported	Median age: 44 (5-85) Males: n=150 Females: n=173 Race/ethnicity: Sicilians	Challenge: 1 g lactose/kg was administered to children weighing 25 kg hydrogen breath test; a standard dose of 25 g was given to all the other subjects, suspended in 250 to 300 ml of water Hydrogen breath test	Overall: 117/323 (36%) Subgroup: Age **Years** **n/N (%)** 6-16 17/72 (23) 17-64 54/141 (38) 65-85 46/110 (42) Self-reported milk-intolerant: 31/49 (63%)

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
	tolerants & intolerants Inclusion/exclusion: known intestinal disease, episodes of diarrhea, consumption of antibiotics or laxatives during the 3 weeks prior to the investigation			Only 5/49 (10%) experienced symptoms post challenge
Farup, 2004[12] Norway	N=187 (IBS Group n=82, Controls n=105) Subject selection: A population-based, case-controlled, health study. Persons with IBS (Rome II criteria) and alarm symptoms were invited to follow up. Also invited were a group of healthy Norwegians to participate in the study as a control group. Exclusion: organic disease	Mean age: 47 Males: n=49 Females: n=138 Race/ethnicity: Norwegians	Challenge: 25 g lactose Hydrogen breath test	Overall: 7/179 (3.9%, 95% CI 1.6%-7.9%) Subgroups (after challenge) IBS group: 3/74 (4.1%) Controls: 4/105 (3.8%) NS
Johnson, 1978[30] USA	N=109 Sample: Native Americans with full and mixed blood from various tribes from the American Great Basin and South West Excluded: subjects with diabetes, or a recent history of diarrhea or intestinal surgery	Mean age: >18 years Males: NA Females: NA Race/ethnicity: Native Americans	Challenge: 50 g lactose/250 ml water Hydrogen breath test	Overall: 98/109 (90%) Subgroup Full-blooded: 92/100 (92%) European admixture: 3/6 (50%)
Ladas, 1991[15] Greece	N=150 (baseline symptoms n=43) Subject selection: Greek children by their teacher-assigned number Exclusion: One child was excluded from the study because of a known milk allergy (atopic dermatitis).	Mean age: NA (5-12) Males: n=72 Females: n=78 Race/ethnicity: Greeks	Challenge: 2 g lactose/kg to a maximum of 50 g or 0.240 L of milk Hydrogen breath test	Overall: 68/144 (47.2%) Subgroups History of symptoms: 27/43 (62.8%)

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
Maggi, 1987[17] Uruguay	N=200 Subject selection: randomly selected volunteer subjects were prospectively studied Inclusion/exclusion: NA	Mean age: NA (0-86) Males: n=100 Females: n=100 Race/ethnicity "White": n=184 "Black": n=16	Challenge: 2 g lactose/kg body weight or 50 g lactose/m^2 body surface Hydrogen breath test	Overall: 113/200 (56.5%) Subgroups In subjects > 20 year old: 78/120 (65%) **Age Group** **n/N (%)** 0-4 5/20 (25) 5-9 8/20 (40) 10-14 15/20 (75) 15-19 7/20 (35) 20-29 14/20 (70) 30-39 16/20 (80) 40-49 9/20 (45) 50-59 16/20 (80) 60-69 10/20 (50) >70 13/20 (65) **Race** **n/N (%)** White 69/109 (63) Black 9/11 (82)
Rao, 1994[44] USA	N=97 (or 98) Subject selection: randomly selected volunteers from the U.S. Army, senior citizens' centers, nursing homes, and a university	Mean age: NA (20-89) Males: n=48 Females: n=50 Race/ethnicity White: n=46 (north central European descent) Black: n=52 (African descent)	Challenge: 16.5 g lactose (360 ml milk) Hydrogen breath test	Overall: 34/98 (34.7%) Subgroups **Age group (yrs) Race/Sex n (%)** <50 (n=58) White males 1 (9) White females 3 (20) All Whites 4 (15) Black males 8 (40) Black females 3 (27) All Blacks 11 (36) Total for age group 15 (26) X^2 Race P=0.1. Sex P>0.05. ≥50 (n=40) White males 7 (13) White females 3 (25) All Whites 4 (20) Total for age group 19 (46) All ages all Blacks 52 (50) All ages all Whites 46 (17) All ages all males 48 (33) All ages all females 50 (36) Total for all age groups 34 (35) X^2 Race P<0.001. Sex P> 0.3.

Table 5. Prevalence of lactose malabsorption by challenge (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Challenge Methods	Prevalence of Lactose Malabsorption
Seakins, 1987[20] Samoa, New Zealand, Cook Islands	N=207 Subject selection: Samoan children were studied in four locations, two in W. Samoa and two in New Zealand. White children were studied in the Cook Islands and New Zealand. Inclusion/exclusion: NA	Mean age: NA (6-13) Males: n=NA Females: n=NA Race/ethnicity Somoans: n=139 Whites: n=68	Challenge: 10 g lactose/100 ml orange flavored, carbohydrate-free cordial Hydrogen breath test	Overall: 74/207 (35.7%) Subgroups Samoans: 65/139 (46.8%) Whites: 9/68 (13.2%)
Schirru, 2007[45] Italy (Sardinia)	N=383 Subject selection: hydrogen breath testing and genotyping of the C/T-13910 variant were performed in 392 patients in Cagliari, Italy Exclusion: celiac disease, milk allergy, Crohn's disease	Mean age: NA (3-19) Males: n=184 Females: n=208 (Number of females, males, and age range are from the original cohort of 392 subjects) Race/ethnicity: Sardinians	Challenge: 2 g/kg body weight to a maximum of 50 g Hydrogen breath test	Overall: 272/383 (71%) Subgroups **Age (yrs): 3, 4 | 5, 6 | 7** n/N (%) 10/34 (29) | 16/43 (37) | 29/45 (64) **Age (yrs): 8 | 9 | 10, 11** n/N (%) 30/39 (77) | 39/45 (87) | 52/63 (84) **Age (yrs): 12-14 | 15-19** n/N (%) 55/66 (83) | 41/48 (85)
Socha, 1984[22] Poland	N=275 Subject selection: healthy Polish adolescents & adults Inclusion/exclusion: NA	Mean age: 29.1 (16-59) Males: n=61 Females: n=214 Race/ethnicity: NA	Challenge: 50 g lactose/400 ml water Hydrogen breath test	Overall: 103/275 (37.5%)

Table 6. Prevalence of hypolactasia

Study	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Hypolactasia
Asymptomatic at baseline				
Newcomer, 1967[18] US	N=100 Subject selection: Healthy Caucasians Exclusion: Intolerance to milk and/or GI symptoms	Mean age: 38.5 (20-63) Males mean age: 37 (20-63) Females mean age: 40 (21-62) Males: n=50 Females: n=50 Race/ethnicity: Caucasians	Biopsy	Overall (≤0.5 U): 6% (95% CI 1.3%-10.3%)
Asymptomatic and symptomatic at baseline				
Ferguson, 1984[50] UK	N=406 Subject selection: 1) retrospective evaluation of White, adult subjects who had had a jejunal biopsy performed (n=150) 2) non White British (n=20) 3) investigated because of diarrhea after gastric surgery (n=36) 4) subjects with irritable bowel syndrome (n=200) Inclusion/exclusion: For the 150 White British sample only those that had no significant intestinal disease; all had normal histopathic jejunal biopsy	Mean age: NA Males: NA Females: NA Race/ethnicity: "White" British, and non White British (Indian, Chinese, Black, Arab)	Biopsy	Groups: White British adults without GI disease: 7/150 (4.7%) Non White British: 15/20 (75%) Diarrhea after gastric surgery: 3/36 (8%) IBS group: 16/200 (8%)
Lebenthal, 1981[51] USA	N=156 Subject selection: in a case-controlled study, White children (n=95) with recurrent abdominal pain, plus 61 age- and race-matched Controls who had undergone diagnostic intestinal biopsies primarily for chronic diarrhea Inclusion: diagnosis of recurrent abdominal pain	Mean age: NA (6-14) Males: NA Females: NA Race/ethnicity: White	Biopsy	Overall: 24/87 (27.6%) Subgroups White children: 8/26 (31%) Controls: 16/61 (26.4%)

Table 6. Prevalence of hypolactasia (continued)

Study	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Hypolactasia
Welsh, 1970[53] USA	N=250 Sample: Intestinal specimens from patients without celiac sprue. Inclusion/exclusion: NA	Mean age: NA (2-81) Males: n=169 Females: n=81 Race/ethnicity White: n=209 Black: n=39 American Indian: n=2	Biopsy	Overall (duodenojejunal): 85/250 (34%) Overall (isolated lactase deficiency (Billroth II procedures)): 9/250 (3.6%)
Symptomatic at baseline				
Pfefferkorn 2002[52] US	N=224 (patients with IBD n=112, patients with chronic abdominal pain n=112) Sample: retrospective and descriptive analysis of pediatric and adolescent patients with IBS were compared to a random sample of age- and gender-matched controls who were being evaluated for abdominal pain Inclusion/exclusion:	Mean age (IBS): 12.7 Mean age (controls): 12.4 (1.9-18.7) Males: n=60 Females: n=52 Race/ethnicity White: n=103 Black: n=9	Biopsy	Overall: NA Subgroups IBS: 45/112 (40%) Chronic abdominal pain: 34/112 (30%) P=0.16 Among 112 with IBD Whites: 38/103 (37%) African Americans: 7/9 (78%)

Table 7. Prevalence of adult-type hypolactasia genotype

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Hypolactasia
Asymptomatic and symptomatic at baseline				
Almon, 2007[55] Sweden	N=1,082 Subject selection: randomly selected children (n=690), and elderly, nonrandomly selected subjects (n=392) Inclusion/exclusion: NA	Mean age: (children were aged either 9 or 15; adults were born between 1920-1932) Males: NA Females: NA Race/ethnicity: Swedes ("Caucasians," "non-Caucasians")	Blood genotyping	Overall (C/C): 117/1082 (10.8%) Subgroups Genotype: C/C; C/T n/N (%); T/T Children: 97/690 (14); 274/690 (40); 319/690 (46) Adults: 20/392 (5); 166/392 (42); 206/392 (53) Caucasians: 61/635 (10); 259/635 (41); 307/635 (48) Non Caucasians: 36/55 (65); 15/55 (27); 4/55 (7)
Anthoni, 2007[158] Finland	N=1,900 Subject selection: Finnish adults attending lab investigations in primary health clinic Inclusion/exclusion: NA	Mean age: "working age" Males: NA Females: NA	Blood genotyping	Overall: 342/1,900 (18%) Subgroups Genotype; History of GI complaints n/N (%); P value C/C: 341/1900 (18); 84/348 (24); <0.05 C/T: 901/1900 (47); 148/348 (43); NS T/T: 658/1900 (35); 116/349 (33); NS Total: 1900 (100); 348 (100); --
Ennattah, 2004[57] Finland	N=234 Subject selection: Finnish army male recruits and men of similar age who had postponed their military service not related to health Inclusion/exclusion: NA	Mean age: NA (18.3-20.6) Males: n=234 Females: n=0 Race/ethnicity: Finns	Blood genotyping	Overall (C/C): 40/234 (17.1%)

Table 7. Prevalence of adult-type hypolactasia genotype (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Hypolactasia
Ennattah, 2005[29] Finland	N=564 Subject selection: cross-sectional, cohort study of population-based women (n=453), women with osteoporotic fractures (n=52), and a control group of women without osteoporosis (n=59) Inclusion/exclusion: Historical lactose intolerance (n=72)	Overall mean age: 70 (62-85) Mean age (pop-based cohort): 69 (62-78) Males: n=0 Females: n=564 Race/ethnicity: Finns	Blood genotyping	Overall: Genotype: C/C; C/T n/N (%); T/T 81/453 (17.9); 212/453 (46.8); 160/453 (35.3)
Gugatschka, 2007[91] Austria	N=239 Subject selection: Men from a population based cohort were invited into study Exclusion: liver or kidney disease, primary hyperparathyroidism, long-term use of corticosteroids, other possible causes of secondary osteoporosis, consumption of bone-active meds, severe nicotine or alcohol abuse	Mean age: 61 (50-85) Males: n=239 Females: n=0 Race/ethnicity: Austrians	Blood genotyping	Overall: Genotype: C/C; C/T n/N (%); T/T 65/239 (27); 131/239 (55); 43/239 (18)
Lehtimäki, 2006[59] Finland	N=3596 (in 1980) Subject selection: prospective, cross-sectional cohort study of randomly selected Finnish children (n=3,596) in 1980, with reexamination in 1983, 1986, and 2001 (after a 21-year followup period) Inclusion/exclusion: NA	Mean age: 10.5 (3-18) (1980) Males: n=1,015 (2002) Females: n=1,250 (2002) Race/ethnicity: Finns	Blood genotyping	Overall (2002): Genotype: C/C; C/T n/N (%); T/T 399/2265 (17.6); 1106/2265 (48.9); 760/2265 (33.6)

Table 7. Prevalence of adult-type hypolactasia genotype (continued)

Author, Year Country	Number Subject Selection Inclusion/Exclusion	Subject Characteristics	Diagnostic Methods	Prevalence of Hypolactasia
Piepoli, 2007[60] Italy (Sardinia and Apulia)	N=254 (there were also 124 subjects with colorectal cancer, but not reported) Subject selection: two different healthy populations were randomly collected: unrelated Apulians and Sardinians Inclusion/exclusion: NA	Mean age: 31.9 (1-73) Males: n=194 Females: n=60 Race/ethnicity: Italians	Blood genotyping	Overall: C/C: 214/254 (84) C/T: 37/254 (14.6) T/T: 3/254 (1)
Schirru, 2007[45] Italy (Sardinia)	N=383 Subject selection: hydrogen breath testing and genotyping of the C/T-13910 variant were performed in 392 patients in Cagliari, Italy Exclusion: celiac disease, milk allergy, Crohn's disease	Mean age: NA (range 3-19) Males: n=184 Females: n=208 (Number of females, males, and age range are from the original cohort of 392 subjects) Race/ethnicity: Sardinians	Blood genotyping	Overall: 344/383 (89.8%) Subgroups Age: 3, 4 / 5, 6 / 7 / 8 C/C n/N (%): 31/35 (89) / 39/43 (91) / 40/45 (89) / 35/39 (90) Age: 9 / 10, 11 / 12-14 / 15-19 C/C n/N (%): 42/45 (93) / 56/62 (90) / 59/66 (89) / 42/47 (90)
Symptomatic at baseline				
Rasinperä, 2004[61] Finland	N=329 Subject selection: Children undergoing upper GI endoscopy because of abdominal complaints Exclusion: children receiving chemotherapy, with GI anomalies, or villous height to crypt depth ratio of < 2:1	Mean age: 8.5 (0.1-20.2) Africans: 6.9 (0.1-15.6) Finns: 9 (0.6-20.2) other Whites) 6.9 (1.9-10.9) Males: n=162 Africans: n=31 Finns: n=125 other Whites: n=6 Females: n=167 Africans: n=34 Finns: n=127 other Whites: n=6 Race/ethnicity: Africans (n=65); Finns (n=252); other Whites (n=12)	Blood genotyping	Overall (C/C): 108/329 (32.8%) Subgroups Finns: C/C 37/252 (14.7); C/T 137/252 (54.4); T/T 78/252 (31.0) Africans: C/C 62/65 (95.4); C/T 3/65 (4.6); T/T 0/65 (0) Other Whites: C/C 9/12 (75.0); C/T 2/12 (16.7); T/T 1/12 (8.3)

Key Question 2. What are the health outcomes of dairy exclusion diets?

Association Between GI Symptoms and Dairy Exclusion Diets

We identified no studies that addressed the long-term impact (>1 month) of dairy exclusion diets on GI symptoms in the general population, vegans, or those diagnosed with LI or LM. Studies that reported symptoms in patients with milk allergies, IBS, or other diseases were beyond the scope of our review. In Key Questions 3 and 4 we report short-term GI outcomes from blinded RCTs among subjects with diagnosed LI or controls fed short-term diets containing varying doses of lactose or lactose free diets. We found low levels of indirect evidence that populations susceptible to LI avoid dairy consumption, presumably in an effort to reduce dairy induced GI symptoms. Postmenopausal Austrian women with TT genotype (lactase persistence) had lower odds of aversion to milk consumption than women with C/C genotype.[68,69] Among children who avoided milk, those diagnosed with LI had much greater odds of milk related symptoms.[76]

Association Between Milk Intake With Genetic Polymorphism, Lactose Intolerance, or Malabsorption

As noted in Key Question 1, results from genetic association tests consistently reported decreased consumption of milk (often on the order of twofold lower) in adults with the C/C genotype compared to those with at least one T allele.[56,57,59,61,91] These differences were smaller in healthy children.[59] The relative differences in calcium intake from all dairy and overall calcium intake were smaller than the differences in milk consumption.[29,57,59,91] All of these studies were from populations in Finland with generally high dairy consumption, except for one study in Austrian men where milk consumption was low in all men.[91] The Finnish Cardiovascular Risk in Young Finns Study demonstrated that those with C/C genotype had lower than recommended calcium intake among young women (crude OR 1.91, 95 percent CI 1.12; 3.23) and men (crude OR 2.00, 95 percent CI 1.36; 2.95).[70] Young women with C/C genotype had a 524 percent increase in odds of following a lactose free diet (OR 6.24, 95 percent CI 3.46; 11.24).[70] Young men with C/C genotype had a 144 percent relative increase in odds of a lactose free diet when compared to those with T/T genotype (OR 2.44, 95 percent CI 1.22; 4.87).[70]

Children and adults with self reported symptoms of milk intolerance and diagnosed LM reported (or were assumed to be consuming) lactose free or low lactose diets.[59,65-67] The association was more consistent for women.[68,69] The association may diminish with aging.[71,72] The American prospective **"**Project EAT: Eating Among Teens" study reported that adolescents with self-perceived lactose intolerance reported decreased dietary calcium intake during the transition to young adulthood.[73]

Association Between Dairy Exclusion Diets and Bone Health

We identified 55 publications of observational studies of 223,336 subjects (Appendix Table D1) that examined the association between lactose intake or factors associated with low lactose

intake (i.e., diagnosis of LI/LM or biopsy or genetic test association for lactase nonpersistence in the absence of specific documentation of the amount of lactose intake) on bone health including clinical (fracture) and intermediate outcomes (osteoporosis, bone mineral density, and content). The absence of specific documentation of the amount of lactose consumed over long periods of time hampered synthesis so indirect associations between bone outcomes and proxy variables for lower lactose consumption were assessed. We identified seven RCTs of 1,207 children, and two RCTs of adult women[62,63] that demonstrated causal effect of lactose intake on bone health. African American women were enrolled in one study.[64]

Sample sizes varied from a minimum of 19 to a maximum of 77,761 subjects, average = 4,06140,61±12,451 subjects. We identified 13 observational studies of 9,577 children or adolescents with an average sample size of 737±1,146 subjects.[59,70,73,76,89,95-99,159-161]

Adult men and women (N = 80,726) were examined in 11 publications with an average sample size of 7,339±14,826 subjects.[5,65,67,83,88,90,92,94,100,162,163] Adult men (N=751) were examined in three publications with an average sample size of 250±24.[57,66,91]

The majority of the studies included women. We identified 28 publications of 132,282 women with an average sample size of 4,724±14,707.[29,64,68,69,71,72,77-82,84-87,93,164-174]

The majority of the studies (N=32) were cross-sectional evaluations that included on average 1,364 subjects. From 55 publications identified, 14 studies were prospective design, seven were case-control studies, one was a meta-analysis of the individual subject data, and one was a prospective observation of the placebo arm in an RCT. The majority of the studies were sponsored by grants from nonprofit resources, 29 studies enrolled an average of 5,929±15,418 subjects. Few (N=7) studies reported combined support from industry and grants, and one study was supported by industry alone. A large proportion of the studies (18/55) did not provide any information about funding sources.

U.S. studies represented 27 percent of all included studies (15/55) and enrolled an average of 7,324±19,795subjects. Studies from North European countries constituted 30 percent of the publications (seven from Austria, ten from Finland, and one from Sweden). Studies from the United Kingdom represented 6 percent of all eligible (3/55) but had larger sample sizes averaging around 25,475±20,363. Asian populations were examined in five studies; two were conducted in Taiwan, one in Hong Kong, one in China, and one in Japan. African American women were enrolled in one study.[64] Other publications either did not report race or ethnical distribution of the subjects or enrolled predominately Caucasians.

Lactose metabolism was addressed in 29 publications.[5,29,57,59,64-69,71,72,88,91,92,94,96,98-100,159,162,164-170] The wide variety of definitions of milk intolerance and absence of the gold standard to diagnose LI hampered synthesis of evidence. Authors defined self reported symptoms as “perceived milk intolerance”[99] or relied on clinical diagnosis that was made based on a positive hydrogen LI test and self reported symptoms after dairy consumption.[66,91,92,100,168] Authors assessed symptoms during or after oral LI tests in few studies.[5,64,166,167]

Trained interviewers who were blinded to the results of oral LI tests assessed symptoms in one study.[72] Two studies used blood glucose examination after oral lactose intake to diagnose malabsorption.[162,170] Several studies obtained a hydrogen breath test after oral lactose intake without evaluating the symptoms of intolerance.[71,98,164,165,169]

One early study defined LI as positive oral lactose tolerance tests, positive glucose tolerance tests, and jejunal biopsy with impaired lactase activity.[94] The remaining 23 publications evaluated the outcomes among populations with different dairy intake but unknown lactose

metabolism.[76-87,89,90,93,95,97,160,163,171-174] Randomized trials examined the effects of increased dairy administration in populations with baseline low lactose intake.

We synthesized the evidence of the association between lactose diet and metabolism on clinical (fracture) and intermediate outcomes (osteoporosis, bone mineral density [BMD], and content) in children and adults. We provided the methodological characteristics of the studies when differences in results could be contributed to external or internal validity of the studies.

Association Between Lactose Intake and Metabolism and Bone Fractures

A low level of inconsistent evidence was available from observational studies that low milk consumers had fractures more often than higher milk consumers (Table 8). There are no data according to race. Observational studies with different quality provided low level evidence that childhood milk avoidance was associated with increased risk of bone fractures. Adults with C/C genotype, symptoms of milk intolerance, or diagnosed LM had reduced lactose intake and increased odds of bone fracture. One large cohort reported that vegans had an increased relative risk of fractures. The effects of lactose free or low lactose diet were more evident in women.

Diet

We found a low level of evidence that children who avoid milk intake had increased odds of bone fractures (Table 8).

The association between lactose intake and bone fracture was examined in 13 publications.[76-88] The Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) compared risk of fracture among vegans and dairy consumers (Table 9).[90]

Children. Low levels of evidence from two industry sponsored studies of prepubertal children from New Zealand found a significant association between lactose free diets and increased odds of bone fractures.[76,89] Prepubertal children with a history of long-term milk avoidance had greater than a threefold increase in odds of the annual incidence of distal forearm fracture (age adjusted odds ratio 3.59, 95 percent CI 1.77; 7.29).[76] Age adjusted odds of history of any fracture were four times higher (OR 4.13, 95 percent CI 1.61; 10.56) among children with lactose free diets when compared to the general population.[89]

Adults. We found a low level of inconsistent evidence in three studies of 44,552 adults that those with low lifetime or childhood milk intake had increased odds of any or osteoporotic fracture.[80,83,88] The largest meta-analyses of individual data from 39,563 adults, participants in the European Vertebral Osteoporosis Study (EVOS/EPOS), the Canadian Multicentre Osteoporosis Study (CaMos), the Dubbo Osteoporosis Epidemiology Study (DOES), the Rotterdam Study, the Sheffield Study, and a cohort from Gothenburg, demonstrated a borderline nonsignificant 10 percent increase in relative risk of osteoporotic fracture in those who consume less than one glass of milk per day (multivariate adjusted RR 1.10, 95 percent CI 1.00; 1.21).[88] The adjustment for body mineral density, however, attenuated the association to nonsignificant.

Women. Low level evidence from nine publications of 111,485 adult women suggested an inconsistent increase in risk of fracture in association with low dairy intake.[77-79,81,82,84-87]

Variability in definitions of lactose intake and types of fracture contributed to inconsistency in the results of the studies. All studies found increased odds of fracture in women with lower dairy intake; however, only five reported a significant association. For instance, an American

study of 5,398 college alumnae, 2,622 former college athletes, and 2,776 non-athletes found a 92 percent increase in multivariate adjusted odds of the first fracture after 40 years of age in low milk consumers when compared to the rest of the population (OR 1.92, 95 percent CI 1.15;3.16).[79] The third National Health and Nutritional Examination Survey demonstrated that older women with dairy intake of less versus more than two servings per day had greater crude odds of osteoporotic fracture.[85] The European Mediterranean Osteoporosis Study showed that women with low lifetime intake of milk had 46 percent increased relative risk of hip fracture (RR 1.46, 95 percent CI 1.21; 1.76).[82]

In contrast, the Nurses' Health Study of 77,761 women who had never used calcium supplements did not detect a significant association between milk or dairy calcium intake and risk of hip fracture at 12 years of followup.[84] Moreover, the same study reported a 93 percent increase in relative risk of hip fracture among women with dairy calcium intake of >550 mg/day versus <175 mg/day (multivariate adjusted RR 1.93, 95 percent CI 1.09; 3.42). Elderly female participants in the Study of Osteoporotic Fractures, who rarely or never consumed dairy calcium during their adolescence, had a 77 percent increase in relative risk of fractured proximal humerus (multivariate adjusted RR 1.77, 95 percent CI 1.12; 2.80) with no differences in risk of fractured distal forearm.[77] Three studies did not find a significant association between lifetime[81,87] or adolescent milk intake[78] and odds of bone fracture.

Men. One meta-analysis of individual data from 15,825 male participants in the EVOS/EPOS, CaMos, DOES, Rotterdam Study, and Sheffield Study, and a cohort from Gothenburg, did not detect a significant association between any osteoporotic or hip fracture in men.[88]

Type of fracture. Low lactose intake was associated with a history of any fracture in prepubertal children and elderly women (Figure 3).[80,86,87,89] The association between low lactose intake and risk of hip fracture was significant in two studies of seven that examined this relationship (Figure 4).[78,79,81-84,88]

Osteoporotic fractures were not associated with lactose intake in the three studies that examined the relationship (Figure 5).[85,86,88]

Dairy calcium intake. Evidence from published studies did not suggest a significant association between dairy calcium intake and bone fractures. Low calcium intake was not associated with fracture in 50 prepubertal children (Appendix Table D3 and Figure 6),[89] 960 Italian women,[81] or 4,342 adults from the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-Up Study cohort.[174]

Vegan diet. We found one study, the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford), that compared relative risk of bone fracture among vegan vegetarians (lactose free diet) with meat and dairy consumers (Table 10).[90] Multivariate adjusted relative risk of incident fracture of bones other than the digits or ribs was 30 percent higher in vegan adults (RR 1.30, 95 percent 1.02; 1.66) but not significant in women or men separately.

Genetic Polymorphism

A single nucleotide polymorphism of the LCT gene at chromosome 2q21-22 in association with fractures was examined in five publications.[29,65,68,69,91]

Children. We did not find studies that examined bone fractures in children with genetic polymorphism.

Women. Evidence of the association between bone fracture and genetic polymorphism from three studies of 895 postmenopausal women was inconsistent in direction and effect size (Table 11).[29,68,69]

A cross sectional Austrian study demonstrated that women with TT genotype had reduced crude odds of fracture (OR 0.26, 95 percent CI 0.13; 0.54).[68] Another smaller prospective Austrian study, however, did not find a significant association between genetic polymorphism with interim vertebral or nonvertebral bone fractures.[69] In contrast, a Finnish study reported greater crude odds of any and nonvertebral fractures in women with TT genotype when compared to C/C genotype.[29] The authors did discuss why their results showed negative association between C/C genotype and bone fractures. They did not calculate odds ratios but compared fractures in three categories of genotype (TT, C/C, and TC). Authors reported a nonsignificant p value from χ^2 tests, and concluded no differences in fractures in relation to genetic pattern.[29]

Adults. One population-based study "Vantaa 85+" of 601 Finnish elderly found that those with C/C genotype had a fourfold increase in crude odds of hip (OR 4.22, 95 percent CI 2.16; 8.26) and nearly threefold increase in crude odds of wrist fracture (OR 2.82, 95 percent CI 1.42; 5.59) when compared to TT genotype.[65]

Men. The Austrian Study Group on Normative Values on Bone Metabolism did not find a significant association between genetic polymorphism and bone fracture in elderly men.[91]

Lactose Intolerance

We synthesized the evidence with the exact definitions of lactose intolerance that were obtained by the primary investigators in the studies.

Children. Children who avoided drinking cow's milk because of perceived milk intolerance did not have higher rates of fracture when compared to those milk avoiders who did not report symptoms of intolerance (Table 12).[89]

Adults. Austrian men and women with self reported symptoms of lactose intolerance during the hydrogen breath test had twofold increased crude odds of any fracture (OR 1.96, 95 percent CI 1.11; 3.48).[92] Estonian men and women with self reported milk intolerance had increased crude odds of osteoporotic fracture (OR 2.69, 95 percent CI 1.25; 5.78).[67]

Women. Finnish postmenopausal women with lactose intolerance did not have greater risk of any, vertebral, or nonvertebral fracture.[29]

Lactose Malabsorption

We synthesized the evidence of the association between LM that was diagnosed with objective breath hydrogen or blood glucose test and bone fractures (Table 12). As noted above, while we did not have information on dairy intake, we assumed that individuals with documented LM have lower dairy intake than absorbers.

Adults. Austrian adults with positive hydrogen breath test had an increase in crude odds of any fracture when compared to lactose absorbers (OR 2.63, 95 percent CI 1.52; 4.54).[92] Adults with severe LI (ΔH_2 >60ppm) had greater than threefold increase in crude odds of vertebral fractures when compared to lactose absorbers (OR 3.62, 95 percent CI 1.93; 6.79).[92]

Women. We found a low level of evidence that women with LM may have increased risk of bone fractures (Table 8).[164,167,170]

The Finnish Kuopio Osteoporosis Risk Factor and Prevention Study demonstrated that women with positive versus negative lactose tolerance test had 33 percent greater odds of any fracture (multivariate adjusted OR 1.33, 95 percent C 1.08; 1.64) after adjustment for age, body mass index (BMI), number of chronic health disorders, and menopausal and smoking status.[167] Smaller case control studies of women failed to detect significant associations. One Finnish study of 18 elderly women with spinal fragility fractures, 28 elderly women with hip fractures, and 35 population controls did not find differences in crude odds of fracture when women with positive blood glucose tests were compared to those with negative tests.[170] Elderly female malabsorbers from New Zealand did not have greater age adjusted odds of fracture when compared to those with negative breath hydrogen tests.[164]

Association Between Lactose Intake and Metabolism with Osteoporosis

Studies examined different populations, used different definitions of impaired lactose metabolism, and evaluated osteoporosis at different bone sites and with varying fracture definitions. Adults with lactose free or low lactose diets had osteopenia more often (Table 13).

Adults. Two studies addressed the odds of osteoporosis in association with lactose intake and reported different results, depending on ethnicity of the subjects and definitions of exposure. The study of Asian adults in Taiwan did not find a significant association between low milk intake and odds of osteoporosis.[163] The U.S. study reported a significant increase in odds of osteoporosis in adults with LI or LM.[94]

Women. Postmenopausal Taiwanese women with lactose free diets had a fourfold increase in adjusted odds of femoral neck when compared to nonvegan vegetarians (multivariate adjusted OR 3.94, 95 percent CI 1.21; 12.82).[93] Italian adults with symptoms of LI and positive hydrogen test an increase in crude odds of osteopenia.[5] Women with different genetic polymorphism had the same odds of osteoporosis.[29,69]

Two small studies totaling 124 women examined crude odds of osteoporosis by LI and LM status.[168,169] An Austrian study reported a large significant increase in crude odds of idiopathic osteoporosis among malabsorbers (OR 36.56, 95 percent CI 8.02; 166.69) and those with milk intolerance (OR 32.31, 95 percent CI 6.97; 149.75).[168] In contrast, an Italian study of postmenopausal women did not find a significant association between osteoporosis and lactose intolerance or malabsorption.[169]

The magnitude and significance of the association varied, depending on definitions of exposure. Studies did not analyze all levels of exposure, including milk and dairy calcium intake, genetic polymorphism, perceived milk intolerance, and positive tests for lactose maldigestion. To address the issue of correlated definitions of exposure, we analyzed, when possible, the odds of lactose free diet in children and adults with genetic polymorphism or lactose malabsorption.

Association Between Genetic Polymorphism, Milk Intake, or Self Reported Lactose Intolerance

Available evidence suggested that children and adults with self reported symptoms of milk intolerance and diagnosed LM reported lactose free or low lactose diets. Adults with C/C genotype reported reduced milk intake. The association was more consistent for women. The association may diminish with aging.

We identified five publications that examined genetic polymorphism in association with lactose intake.[59,65-67,70] One study of children and adolescence, the Cardiovascular Risk in Young Finns Study, found that dietary intake of milk and milk products was significantly lower for girls with the C/C.[59] The same study did not report significant difference in milk intake among boys (Appendix Table D4). During the transition to young adulthood, however, both genders with C/C genotype did not drink milk (OR 1.86, 95 percent CI 1.34; 2.59 among women and 2.00, 95 percent CI 1.36; 2.95 among men).[70] The odds of following a low lactose or milk free diet at 24-39 years of age were also significantly higher in those with C/C genotype (OR 6.24, 95 percent CI 3.46; 11.24 in females and 2.44, 95 percent CI 1.22; 4.87 in males).[70]

Among adults, one study of Austrian men reported that milk tolerance and consumption were higher in those with TT genetic polymorphism compared to T/C or C/C types.[66] Two studies of adults also reported that those with TT type had greater odds of using milk products (OR 2.06, 95 percent CI 1.38; 3.06)[65] and greater daily milk intake.[67]

Two studies demonstrated smaller odds of positive tests for lactose malabsorption in adults with T/T when compared to C/C genotypes (Figure 7).[66,69]

The odds of self reported symptoms of lactose intolerance were higher in women with C/C genetic polymorphism (Appendix Table D5).[68,69] Men with different genotypes, however, had the same frequency of milk related clinical symptoms.[57,66,91]

Studies demonstrated that children and adults diagnosed with LM had clinical symptoms more often than controls (Appendix Table D5). Adult malabsorbers reported symptoms of LI more often when compared to absorbers (OR 107.98, 95 percent CI 6.34; 1838.99).[5] The association was dose response shaped with a greater than threefold increase in odds of symptomatic LI in adults with moderate (OR 3.58, 95 percent CI 1.43; 9.00) and with a six fold increase in those with severe LM (ΔH_2 >60ppm) when compared to lactose absorbers (OR 6.22, 95 percent CI 2.87; 13.51).[92] Postmenopausal lactose malabsorbers had milk-related clinical symptoms more often; however, the results did not achieve statistical significance.[71,72]

Summary. Observational studies with different quality provided low level evidence that childhood milk avoidance may be associated with increased risk of bone fractures. Selected adult populations with C/C genotype, symptoms of milk intolerance, or diagnosed LM and reduced lactose intake may have increased odds of bone fracture. One large cohort reported that vegan vegetarians had increased relative risk of fractures. The effects of lactose free or low lactose diet were more evident in women.

Association Between Lactose Intake and Metabolism and Bone Mineral Content or Density

We summarize here the results from seven RCTs in children,[101-107] two RCTs of women,[62,63] and 28 observational studies reporting bone mineral density or content.[5,57,66-69,71,72,76,91-93,95-100,159-162,165-167,169,171,172]

The studies suggest that children and adults with lactose free or low lactose diets may have reduced bone mineral content (BMC) and bone mineral density (BMD). The actual differences, however, varied across the studies, depending on the populations, definitions of exposure, time of followup, and measured bones (Table 8).

Diet.

Children. We found a moderate level of evidence from RCTs that increased lactose intake resulted in improved BMC of lumbar spine and femoral neck in prepubertal children with low

baseline milk intake (Table 14). Dairy intervention with 1,794 or 1,067 mg calcium per day for 12 months resulted in significant increases in total body BMC in boys and girls from Hong Kong (Figure 8).[101] This open label trial included 344 boys and girls 10.0 ± 3 years of age with very low baseline milk intake of 35.6 percent of the recommended daily calcium consumption.[101] One RCT that included prepubertal children with very low baseline milk intake of 30.8 percent from that recommended also reported a significant increase in total body BMC after dairy administration that provided 1,200 mg calcium per day.[102] The effect, however, was not significant at 18 months of followup.[102] The U.S.[103] and British[104] RCTs that included only girls consuming half the recommended daily calcium did not demonstrate significant improvement in total body BMC.

The same pattern was seen in BMC of femoral neck. Children with very low baseline calcium intake (36 percent from the recommended) experienced significant increase in BMC.[101] Children that consumed half of the recommended calcium did not have a noticeable increase in BMC (Figure 9).[106,107] The effects of dairy interventions on total hip BMC were significant in all three RCTs that examined the association (Figure 10).

Design, population gender, and baseline milk intake could explain study inconsistencies in increased lumbar spine BMC. Lumbar spine BMC was increased in three RCTs,[101,102,105] while two trials did not report significant changes in this outcome[106,107] (Figure 11). Children from Hong Kong with very low baseline calcium intake had the greatest increase in lumbar spine BMC.[101] This evidence suggests that dairy intervention increased lumbar spine BMC in girls[105] but not in boys[106] because trials did not differ by country (both trials were conducted in Switzerland), baseline milk intake, and design (both trials were double blinded). Neither absolute levels of BMC nor changes from baseline in BMC or BMD differed in boys after dairy intervention (1,607 mg calcium/day) when compared to placebo (747 mg calcium/day) (Appendix Table D6).[106]

The improvement in BMD was less evident. Dairy interventions did not increase BMD in girls in two RCTs that reported absolute levels of the outcome.[103,105] Dairy interventions increased BMD from baseline in one RCT of Finnish girls,[107] while British girls[104] and children from New Zealand[102] or Hong Kong[101] did not have significant changes in BMD (Table 15).

In contrast with RCTs, observational studies (Table 16) reported that children with very low milk intake had reduced BMD compared to the reference population.[76,96,97] Long term milk avoiders had lower BMC.[76,95-97] Studies did not address all confounding factors.

Adults. A low level of evidence in one study suggested that low milk consumers (<4dL/day) had decreased BMD when compared to high milk consumers (>4dL/day).[67]

Women. Inconsistent evidence of the association between low lactose diets and bone outcomes were limited to two RCTs[62,63] and two observational studies.[93,171] Dairy intervention resulted in a short term increase (6 months) in total spine BMD in young women with high adherence to their diet.[62] Intention to treat analysis did not detect a significant improvement in BMD (Table 17). Dairy intervention reduced age related decline over a 3-year period in vertebral bone mineral density in pre-menopausal women.[63] Asian women that followed a lactose free vegan diet had the same BMD as milk consumers (Appendix Table D7).[93,171]

Lactose intolerance. We found low levels of evidence that children and adults with self reported milk intolerance (assumed low dairy intake) had reduced BMC or BMD (Table 8). American children[98] and adolescent girls[99] with LI had an inconsistent reduction in BMC (Table 16). Adults with self reported milk intolerance had a consistent reduction in BMD[5,67,100] and BMC.[5] A small observation of 58 postmenopausal Italian women, however, did not report a

significant difference in BMD in those with symptoms of LI when compared to healthy asymptomatic milk consumers.[169]

Lactose malabsorption. We found low levels of evidence that, when compared to absorbers, children with diagnosed LM (and therefore assumed to be have low dairy intake) had lower BMC.[99] LM in women was associated with inconsistent reduction in BMD[72,166,167,169] with no differences in BMC.[71] The studies of adults did not find a difference in either BMD[5,92,162] or in BMC[5] in malabsorbers compared to the general population.

Genetic polymorphism. We found low levels of evidence that women with C/C genotype had lower BMD when compared to TT genotype.[68,69]

Bone outcomes did not differ by genotype in adults[67] or in men.[57] Bone density did not differ by genotype in either gender (Appendix Table D8). However, one prospective Cardiovascular Risk in Young Finns study demonstrated that at 12 years of followup young men with C/C genotype tended to have greater bone loss when compared to those with T/T genotype (bone mineral density in lumbar spine p=0.081).[161]

Table 8. Association between lactose intolerance and bone outcomes

Exposure	Number of Studies/Patients	Bone Mineral Density (BMD) or Content (BMC)	Level of Evidence	Number of Studies/Patients	Fractures, Osteoporosis or Osteopenia	Level of Evidence
Children						
Diet	7 RCTs/1,207 children (mean age range 7-11 years old) Chan, 1995[103] Bonjour, 1997[105] Cadogan, 1997[104] Lau, 2004[101] Gibbons, 2004[102] Chevalley, 2005[106] Cheng, 2005[107]	Inconsistent increase in BMC of lumbar spine and femoral neck at 12, and 18 months after increased dairy intake. Results did not persist at 24 months of followup	Moderate	2 /100, New Zealand Black, 2002[76] Goulding, 2004[89]	Milk avoiders had increase in adjusted odds by **259 (OR 3.59, 95% CI 1.77; 7.29)- 313% (OR 4.13, 95% CI 1.61; 10.56)**	Low
	4/940 Parsons, 1997[95] Du, 2002[96] Black, 2002[76] Rockell, 2005[97]	BMC Inconsistent reduction in BMC among milk avoiders	Low			
	3/745 Du, 2002[96] Black, 2002[76] Rockell, 2005[97]	BMD Consistent reduction in milk avoiders	Low			
Dairy Ca++	1/152 Vatanparast, 2005[160]	For every additional 1 mg Ca++ for boys, 0.017 g increase in total body BMC NS for girls	Low	Goulding, 2004[89]	NS	Low
Lactose malabsorption	1/291 Matlik, 2007[99]	Inconsistent reduction in BMC	Low			
Lactose intolerance	2/310 Stallings, 1994[98] Matlik, 2007[99]	Inconsistent reduction in BMC	Low	Goulding, 2004[89]	NS among those milk avoiders with perceived LI vs. no symptoms of LI	Low
Genotype	1/358 19168163	During the transition to young adulthood men but not women with C/C genotype tended to have greater bone loss	Low			

Table 8. Association between lactose intolerance and bone outcomes (continued)

Exposure	Number of Studies/Patients	Bone Mineral Density (BMD) or Content (BMC)	Level of Evidence	Number of Studies/Patients	Fractures, Osteoporosis or Osteopenia	Level of Evidence
Adult women						
Diet	2 RCTs/496 adult women (mean age range 28-35 years old) Woo, 2007[62] Baran, 1990[63]	Short term increase (6 months) in total spine BMD in young women with high adherence to increased lactose diet. Reduced decline in vertebral BMD in pre-menopausal women.	Low	9/111,485 Kelsey, 1992[77] Nieves, 1992[78] Wyshak, 1989[79] Tavani, 1995[81] Johnell, 1995[82] Feskanich, 1997[84] Turner, 1998[85] Johansson, 2004[87] Kalkwarf, 2003[86]	Inconsistent evidence that low lifetime milk intake is associated with increased odds of fracture	Low
Dairy Ca++				1/960 Tavani, 1995[81]	NS	Low
Vegan diet	2/443 Lau, 1998[171] Chiu, 1997[93]	BMD in Asian women NS	Low	1/ 26, 749 Appleby, 2007[90]	NS	Low
				1/258 Chiu, 1997[93]	Osteopenia Increased in adjusted odds by 294% **(OR 3.94, 95% CI 1.21; 12.82)**	Low
Lactose malabsorption	1/80 Goulding, 1999[71]	BMC NS	Low	3/11761 Honkanen, 1997[167] Wheadon, 1991[164] Harma, 1988[170]	Inconsistent increase in crude and adjusted odds	Low
	4/13,748 Honkanen, 1997[167] Honkanen, 1996[166] Corazza, 1995[169] Horowitz, 1987[72]	BMD Inconsistent reduction	Low	2/124 Finkenstedt, 1986[168] Corazza, 1995[169]	Osteoporosis Inconsistent increase in crude odds	Low
Lactose intolerance	1/58 Corazza, 1995[169]	BMD NS	Low	1/564 Enattah, 2005[29]	NS	Low
				2/124 Finkenstedt, 1986[168] Corazza, 1995[169]	Osteoporosis Inconsistent increase in crude odds	Low
Genetic polymorphism	2/331 Obermayer-Pietsch, 2004[68] Obermayer-Pietsch, 2007[69]	BMD Consistent reduction among individuals with C/C genotype	Low	3/895 Obermayer-Pietsch, 2004[68] Obermayer-Pietsch,	Inconsistent evidence that women with C/C genotype had	Low

Table 8. Association between lactose intolerance and bone outcomes (continued)

Exposure	Number of Studies/Patients	Bone Mineral Density (BMD) or Content (BMC)	Level of Evidence	Number of Studies/Patients	Fractures, Osteoporosis or Osteopenia	Level of Evidence
				2007[69] Enattah, 2005[29]	increased crude odds of fracture	
				2/637 Enattah, 2005[29] Obermayer-Pietsch, 2007[69]	Osteoporosis NS	Low
Adults						
Diet	1/367 Kull, 2009[67]	BMD Significant reduction in low milk consumers	Low	3/44,552 Cumming, 1994[80] Fujiwara, 1997[83] Kanis, 2005[88]	Inconsistent increase in odds of lifetime or osteoporotic fracture in those with low lifetime or childhood milk intake	Low
				1/404 Shaw, 1993[163]	Osteoporosis NS in those with low milk intake	Low
Dairy Ca++				1/4342 Looker, 1993[174]	NS	Low
Vegan Diet				1/34,696 Appleby, 2007[90]	Increase in adjusted relative risk by 30% **(RR 1.30, 95% CI 1.02; 1.66)**	Low
Lactose malabsorption	1/103 Di Stefano, 2002[5]	BMC NS	Low	1/218 Kudlacek, 2002[92]	Increase in crude odds of overall factures by 163% (**OR 2.63, 95% CI 1.52; 4.54)** and crude odds of verterbral fracture by 262% (OR **3.62, 95% CI 1.93; 6.79)** in those with severe LM	Low
	3/350 Di Stefano, 2002[5] Alhava, 1977[162] Kudlacek, 2002[92]	BMD NS	Low	1/103 Di Stefano, 2002[5]	Osteopenia Increase in crude odds by 677 (OR **7.77, 95% CI 2.20; 27.44)**-959 (OR	

Table 8. Association between lactose intolerance and bone outcomes (continued)

Exposure	Number of Studies/Patients	Bone Mineral Density (BMD) or Content (BMC)	Level of Evidence	Number of Studies/Patients	Fractures, Osteoporosis or Osteopenia	Level of Evidence
					10.59, 95% CI 2.66; 42.20) in LM with LI symptoms	
Lactose intolerance	1/103 Di Stefano, 2002[5]	Reduction in BMC	Low	2/585 Kudlacek, 2002[92] Kull, 2009[67]	Increased in crude odds by 96% (OR **1.96 95% CI 1.11; 3.48)**169% (OR **2.69, 95% CI 1.25; 5.78)**	Low
	3/536 DiStefano, 2002[5] Kull, 2009[67] Segal, 2003[100]	BMD Consistent reduction	Low	Birge, 1967[94]	Osteoporosis Increase in crude odds by 656% (OR **7.56, 95% CI 1.30; 43.98)**	Low
Genetic polymorphism	1/367 Kull, 2009[67]	BMD NS	Low 1/32	Enattah, 2005[65]	Elderly with C/C genotype had 322% increase in crude odds (OR **4.22, 95% CI 2.17; 8.33)**	Low
Adult males			1/601			
Diet				1/15,825 Kanis, 2005[88]	NS	Low
				1/404 Shaw, 1993[163]	Osteoporosis NS in men with low milk intake	Low
Vegan diet				1/7,947 Appleby, 2007[90]	NS	Low
Genetic polymorphism	1/234 Enattah, 2004[57]	BMC NS	Low	1/239 Gugatschka, 2007[91]	NS	Low
	1/234 Enattah, 2004[57]	BMD NS	Low			

Bold = statistically significant

Table 9. Association between low lactose diets and bone fractures

Study	Comparison	Outcome	Estimate	Mean 95% CI)
Black, 2002[76] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Milk avoiders vs. general population	Annual incidence of distal forearm fracture	Age adjusted OR	**3.59 (1.77; 7.29)**
Goulding, 2004[89] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Family members avoiding milk vs. not	History of fracture	Crude OR	1.33 (0.30; 5.88)
	Milk avoiders 0-13 years old vs. general population		Age adjusted OR	**4.13 (1.61; 10.56)**
Johnell, 1995[82] Country: Sweden Women Ca++ intake difference in comparison groups: NR/Y	Low lifetime intake of milk vs. above the low	Hip fracture	Adjusted for age, center, BMI RR	**1.46 (1.21; 1.76)**
	Milk intake >5 glasses/day vs. never or sometimes		Adjusted for age, center, BMI RR	**0.77 (0.66; 0.89)**
Tavani, 1995[81] Country: Italy Postmenopausal women Ca++ intake difference in comparison groups: NR/NR	Milk intake (drinks/week) >7 vs. <7	Hip fracture	Adjusted for age, education, smoking status, total alcohol consumption, and estrogen replacement therapy OR	1.00 (0.60; 1.60)
	Cheese intake, portions/week 4-6 vs. <4			1.20 (0.80; 1.70)
	Cheese intake (portions/week) 4-6 vs. >6			1.00 (0.70; 1.50)
Fujiwara, 1997[83] Country: Japan Adults Ca++ intake difference in comparison groups: NR/NR	Milk intake >5/week vs. <1/week	Hip fracture	Adjusted for age, sex, BMI, alcohol intake, for women-parity RR	0.54 (0.25; 1.07)
Kalkwarf, 2003[86] Country: USA Non-Hispanic, white women Ca++ intake difference in comparison groups: NR/NR	Child milk intake <1 serving/week vs. >I serving/day	Lifetime fracture	Adjusted for age and weight OR	**2.02 (1.13; 3.59)**
		Osteoporotic fracture		**2.25 (1.26; 4.00)**
	Adolescent milk intake: <1 serving/week vs. >I serving/day	Lifetime fracture		1.49 (0.90; 2.46)
		Osteoporotic fracture		1.29 (0.75; 2.19)
	Childhood and adolescence ≤1/week vs. >1/week	Lifetime fracture		**1.60 (1.17; 2.18)**
		Osteoporotic fracture		1.19 (0.83; 1.70)
Kanis, 2005[88] Country: UK Adults Ca++ intake difference in comparison groups: NR/NR	Low milk intake (<1 glass/day) vs. >1 glass/day	Osteoporotic fracture in males	Adjusted for current time, current age, milk intake and milk intake times current age RR	1.11 (0.90; 1.36)
		Osteoporotic fracture in females		1.09 (0.98; 1.22)
		Hip fracture in males		1.50 (0.89; 2.54)

Table 9. Association between low lactose diets and bone fractures (continued)

Study	Comparison	Outcome	Estimate	Mean 95% CI)
		Hip fracture in females		1.09 (0.82; 1.44)
		Osteoporotic fracture in all ages	Adjusted for current time, current age, milk intake and milk intake times current age, and BMD RR	1.06 (0.95; 1.19)
			Adjusted for the same variables as above but not BMD RR	**1.10 (1.00; 1.21)**
		Hip fracture in all ages	Adjusted for current time, current age, milk intake and milk intake times current age, and BMD RR	1.10 (0.83; 1.47)
			Adjusted for the same variables as above but not BMD RR	1.17 (0.91; 1.50)
Johansson, 2004[87] Country: UK Elderly women Ca++ intake difference in comparison groups: NR/NR	Intake of milk (score 0–5) from never, occasional, and 1-2, 3-4, to 5 glasses/day	Fracture	Crude RR	0.91 (0.78; 1.07)
Cumming, 1994[80] Country: Australia Elderly women and men Ca++ intake difference in comparison groups: NR/NR	11.5 units of dairy products/week vs. 0 units at age 20	Fracture	Adjusted for age and sex OR	**3.20 (1.30; 7.70)**
	11.5 units of dairy products/week vs. 0 units at age 50			1.70 (0.70; 4.20)
	11.5 units of dairy products/week vs. 0 units at current age			**2.10 (1.00; 4.70)**
Feskanich, 1997[84] Country: USA Middle aged women Ca++ intake difference in comparison groups: NR/NR	2-6 glasses of milk/week vs. <1	Hip Fractures	Adjusted for age; body mass index; menopausal status and use of postmenopausal estrogen; cigarette smoking; amount of vigorous activity; use of thyroid hormone medication and thiazide diuretics; and alcohol, caffeine, and total energy intakes. RR	1.36 (0.86; 2.16)
	2-6 glasses of milk/week vs. <1	Forearm fractures		1.04 (0.88; 1.23)
	Dairy calcium intake >550/day vs.<175	Hip fractures		**1.93 (1.09; 3.42)**
	Dairy calcium intake >550/day vs.<175	Forearm fractures		1.07 (0.89; 1.30)
	Milk consumption during teenage years 2-6 glasses/ week vs. <1 glass/week	Hip fractures		0.88 (0.56; 1.38)
	Milk consumption during teenage years >3 glasses/day vs. <1 glass/week		Adjusted for questionnaire time period, age; body mass index; menopausal status and use of postmenopausal hormones; cigarette smoking; and adult (1980) milk consumption. RR	0.53 (0.25; 1.16)
	Milk consumption during teenage years 2-6 glasses/ week vs. <1 glass/week	Forearm fractures		1.01 (0.84; 1.21)
	Milk consumption during teenage years >3 glasses/day vs. <1 glass/week			0.96 (0.76; 1.25)

Table 9. Association between low lactose diets and bone fractures (continued)

Study	Comparison	Outcome	Estimate	Mean 95% CI)
Kelsey, 1992[77] Country: USA Older women Ca++ intake difference in comparison groups: NR/NR	Calcium intake from milk in adolescence: rarely or never vs. all others	Fracture of distal forearm	Adjusted for age, poor visual acuity, number of falls in the year before baseline, frequent walking, recent decline in health status, insulin-dependent diabetes mellitus, indicators of neuromuscular weakness RR	1.13 (0.81; 1.59)
		Fracture of proximal humerus		**1.77 (1.12; 2.80)**
	Dietary Ca++ in year before baseline > vs. <5,000 mg/week	Fracture of distal forearm		1.01 (0.78; 1.30)
	Dietary Ca++ in year before baseline > vs. <5,000 mg/week	Fracture of proximal humerus		0.95 (0.65; 1.37)
Turner, 1998[85] Country: USA Older women Ca++ intake difference in comparison groups: NR/NR	Dairy intake < vs. >2 servings/day	Osteoporotic fracture	Crude OR	**65.66 (35.11; 122.80)**
Nieves, 1992[78] Country: USA Middle aged women Ca++ intake difference in comparison groups: NR/NR	Milk intake in adolescence, >7 glasses/week vs. none	Hip fracture	Matching by age and hospital, adjusted for BMI OR	1.10 (0.63; 1.94)
	Ca++mg/day during the last year >1,000 vs. <400		Matching for hospital and age and the following potential confounders: Quetelet index, estrogen use, and presence of chronic disease OR	1.24 (0.59; 2.63)
Wyshak, 1989[79]Country: USA Women Ca++ intake difference in comparison groups: NR/NR	Low milk diet vs. not	First fracture after 40 years of age	Adjusted for current consumption of nonalcoholic carbonated beverages; current consumption of alcoholic beverages; age; current dietary restrictions, smoking history; pregnancy history; currently exercising regularly; and use of hormones for menopausal symptoms OR	**1.92 (1.15; 3.16)**

Bold = statistically significant

Figure 3. Association between milk intake and history of any fracture

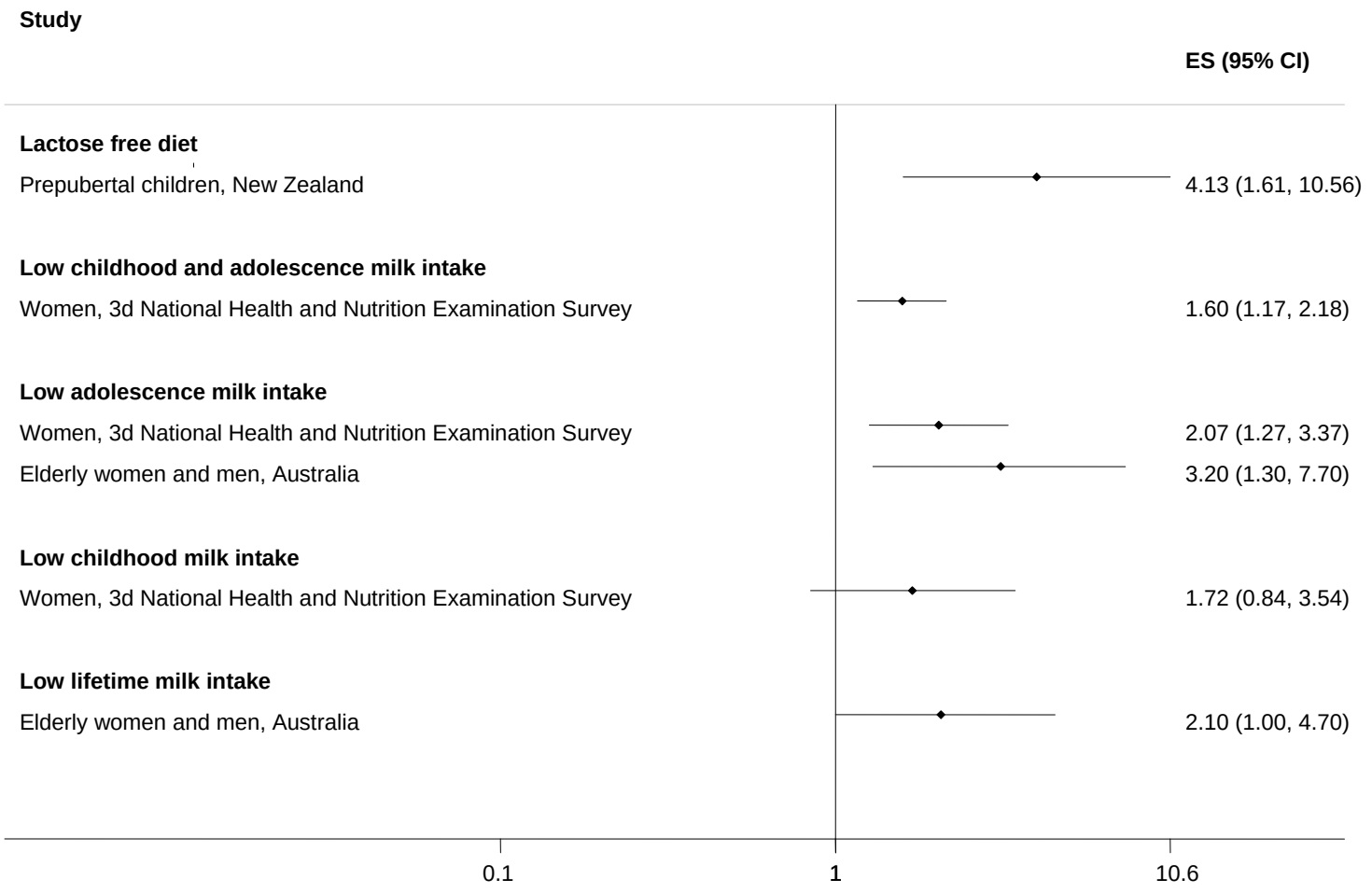
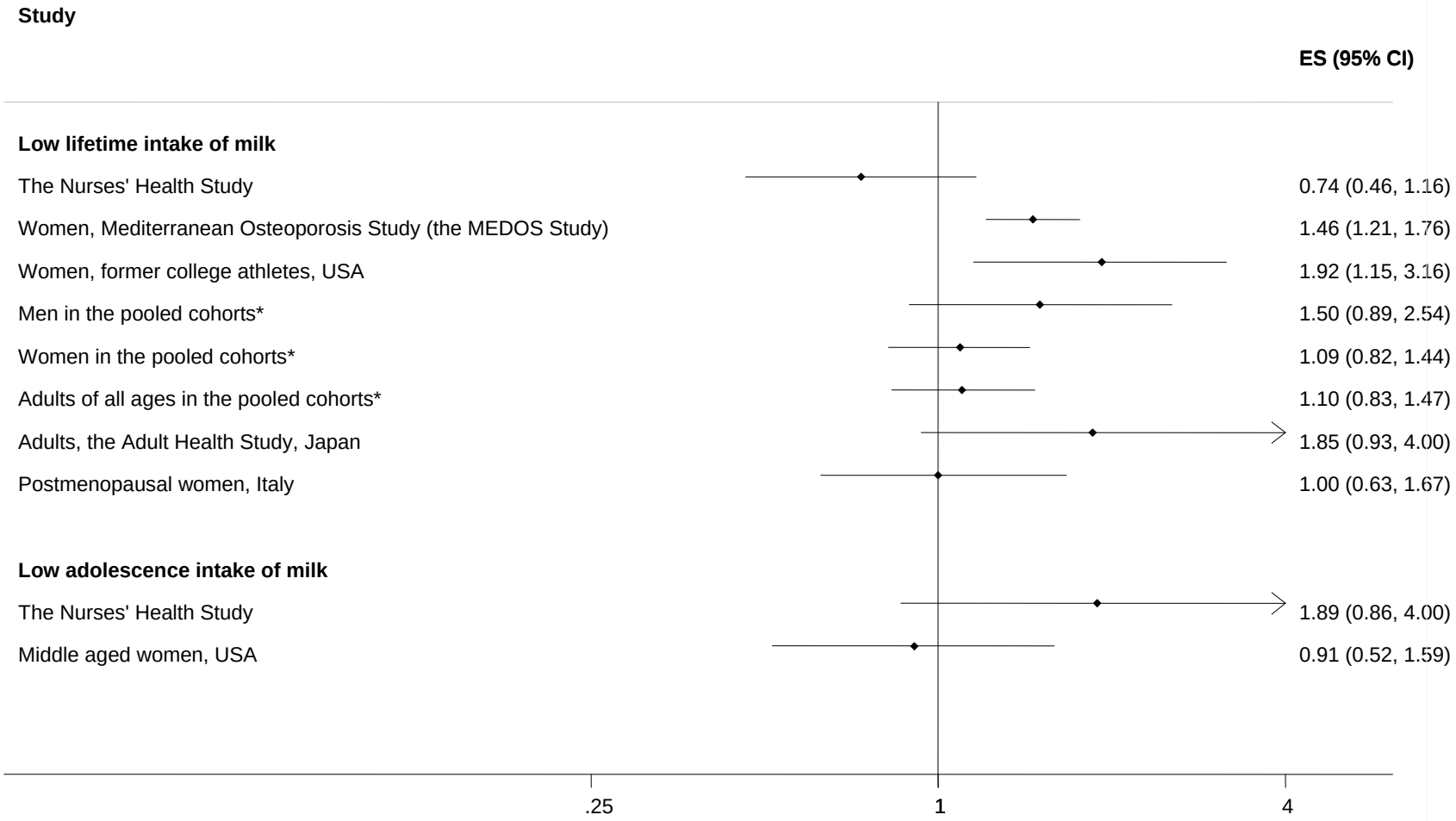
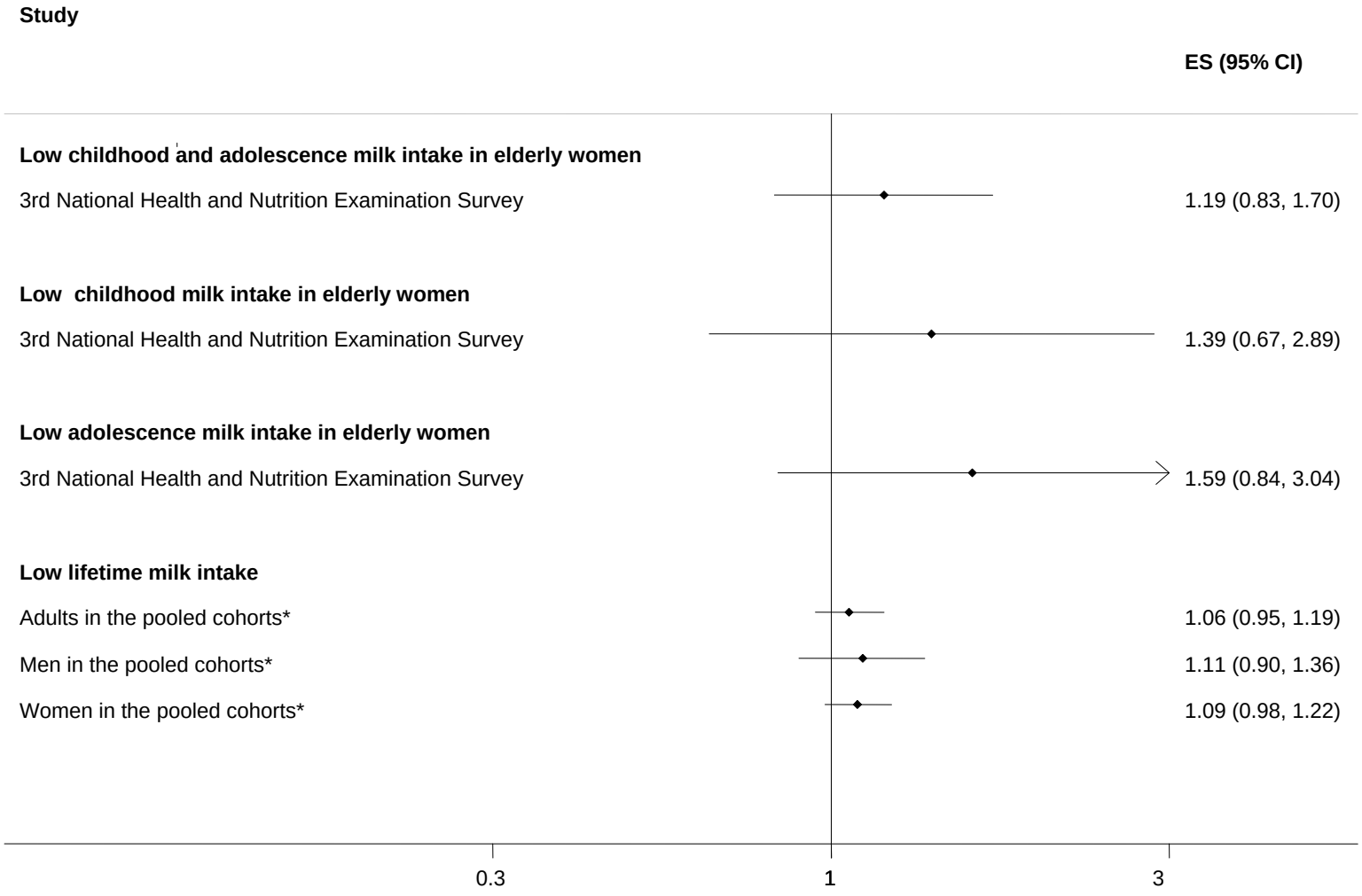


Figure 4. Association between milk intake and hip fracture



* The European Vertebral Osteoporosis Study (EVOS/EPOS study), the Canadian Multicentre Osteoporosis Study (CaMos), the Dubbo Osteoporosis Epidemiology Study (DOES), the Rotterdam Study, the Sheffield Study and a cohort from Gothenburg.

Figure 5. Association between milk intake and osteoporotic bone fractures



*The European Vertebral Osteoporosis Study (EVOS/EPOS study), the Canadian Multicentre Osteoporosis Study (CaMos), the Dubbo Osteoporosis Epidemiology Study (DOES), the Rotterdam Study, the Sheffield Study and a cohort from Gothenburg

Figure 6. Association between dairy calcium intake (mg/day) and bone fractures

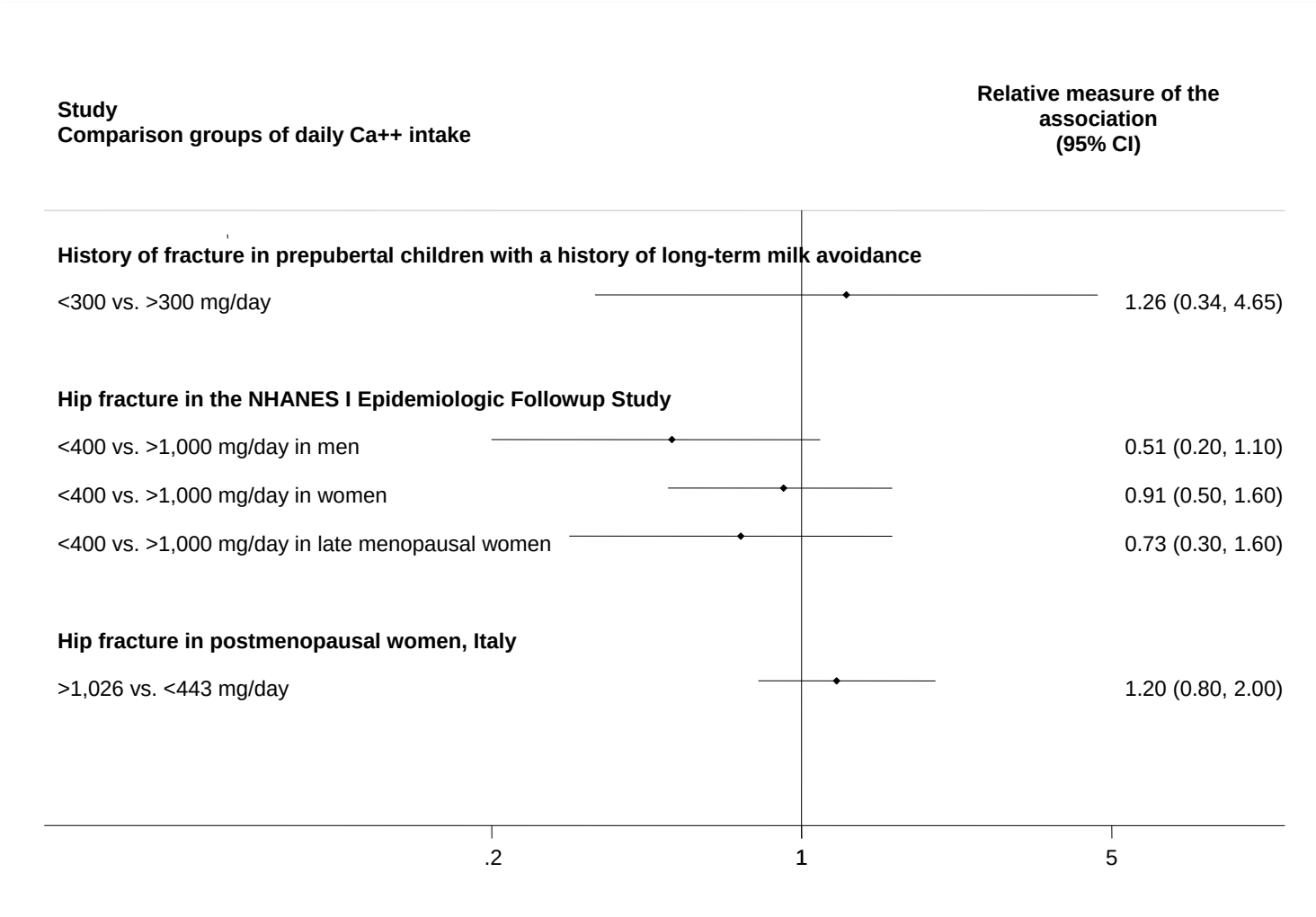


Table 10. Association between vegan diet (lactose free) and incident fracture of bones other than the digits or ribs, results from the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford)[90]

Comparison	Estimate	Mean (95%CI)
Vegan men vs. meat eaters: men	Adjusted for age RR	1.30 (0.85; 2.00)
Vegan women vs. meat eaters women		1.28 (0.95; 1.72)
Vegan adults vs. meat eaters: adults		**1.37 (1.07; 1.74)**
Vegan men vs. meat eaters: men	Adjusted for age, smoking, alcohol consumption, body mass index, exercise, physical activity at work, marital status and for women parity and use of hormone replacement therapy RR	1.19 (0.76; 1.85)
Vegan women vs. meat eaters women		1.21 (0.89; 1.64)
Vegan adults vs. meat eaters adults		**1.30 (1.02; 1.66)**
Vegan men vs. meat eaters men	Adjusted for age, smoking, alcohol consumption, body mass index, exercise, physical activity at work, marital status and for women parity and use of hormone replacement therapy, energy and calcium intake RR	1.20 (0.73; 1.98)
Vegan women vs. meat eaters women		1.05 (0.76; 1.44)
Vegan adults vs. meat eaters adults		1.15 (0.89; 1.49)
Vegan men consuming at least 525 mg/day calcium vs. meat eaters	Adjusted for age, smoking, alcohol consumption, body mass index, exercise, physical activity at work, marital status and for women parity and use of hormone replacement therapy RR	0.80 (0.42; 1.51)
Vegan women consuming at least 525 mg/day calcium vs. meat eaters		0.96 (0.61; 1.51)
Vegan adults consuming at least 525 mg/day calcium vs. meat eaters		1.00 (0.69; 1.44)

Bold = statistically significant

Table 11. Association between genetic polymorphism and bone fractures

Study	Comparison	Outcome	Estimate	Mean (95% CI)
Gugatschka, 2007[91] Country: Austria Elderly male Ca++ intake difference in comparison groups: -21/Y	T/T vs. C/T	Fractures (number)	Crude mean difference	-0.03 (-0.58; 0.52)
	T/T vs. C/C			0.28 (-0.32; 0.88)
Obermayer-Pietsch, 2004[68] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 0.55/Y	T/T vs. C/C	Bone fracture incidence	Crude OR	**0.26 (0.13; 0.54)**
	T/C vs. C/C			**0.37 (0.19; 0.71)**
	T/T vs. TC			0.71 (0.39; 1.27)
Gugatschka, 2007[91] Country: Austria Elderly male Ca++ intake difference in comparison groups: 14/N	C/T vs. C/C	Fractures (number)	Crude mean difference	0.31 (-0.27; 0.89)
Obermayer-Pietsch, 2007[69] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 349/Y	T/T vs. C/C	Interim nonvertebral bone fractures	Crude OR	0.76 (0.14; 4.06)
	T/T vs. C/C	Interim vertebral fractures		1.59 (0.14; 18.36)
Enattah, 2005[65] Country: Finland Elderly Ca++ intake difference in comparison groups: NR/NR	T/T vs. C/C	Fracture of hip	Crude OR	**0.24 (0.12; 0.46)**
		Fracture of wrist		**0.36 (0.18; 0.70)**
	C/T vs. C/C	Fracture of hip		**0.30 (0.17; 0.56)**
		Fracture of wrist		**0.43 (0.23; 0.81)**
	T/T vs. C/T	Fracture of hip		0.78 (0.45; 1.36)
		Fracture of wrist		0.83 (0.49; 1.40)
Enattah, 2005[29] Country: Finland Postmenopausal women Ca++ intake difference in comparison groups: NR/NR	T/T vs. C/C	History of any fracture	Crude OR	**2.12 (1.05; 4.27)**
		Vertebral		3.31 (0.40; 27.61)
		Nonvertebral		**4.14 (2.06; 8.31)**

Bold = statistically significant

Table 12. Association between lactose intolerance or malabsorption and bone fractures

Study	Comparison	Outcome	Estimate	Mean (95% CI)
Symptomatic lactose intolerance				
Goulding, 2004[89] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Symptoms to cow milk vs. none	History of fracture	Crude OR	1.45 (0.44; 4.78)
Enattah, 2005[29] Country: Finland Postmenopausal women Ca++ intake difference in comparison groups: NR/NR	Lactose intolerance vs. none	History of any fracture	Crude OR	1.63 (0.88; 3.01)
		Vertebral		2.45 (0.74; 8.18)
		Nonvertebral		1.51 (0.79; 2.88)
Kudlacek, 2002[92] Country: Austria Adults Ca++ intake difference in comparison groups: NR/NR	Self reported symptoms of LI vs. none	Fracture	Crude OR	**1.96 (1.11; 3.48)**
Kull, 2009[67] Country: Estonia Adults Ca++ intake difference in comparison groups: NR/NR	Self-reported LI vs. none	Fracture occurring after the age of 25	Crude OR	**2.69 (1.25; 5.78)**
Diagnosed with objective tests lactose malabsorption				
Honkanen, 1997[167] Country: Finland Perimenopausal women Ca++ intake difference in comparison groups: -280/Y	Positive vs. negative lactose tolerance test	A fracture since age of 15	Crude OR	**1.39 (1.18; 1.63)**
		Any fracture		**1.33 (1.09; 1.62)**
		Wrist, radius		1.05 (0.69; 1.59)
		Any fracture	Adjusted for age, BMI, number of chronic health disorders, menopausal status (postmenopausal/other), and smoking status OR	**1.33 (1.08; 1.64)**
		Wrist		1.04 (0.67; 1.60)
		Nonwrist		1.21 (0.81; 1.80)
Wheadon, 1991[164] Country: New Zealand Elderly New Zealand women with hip fractures Ca++ intake difference in comparison groups: 317/N	Malabsorbers vs. none (age matched controls)	History of fracture	Age matched OR	0.90 (0.21; 3.82)
	Malabsorbers vs. none (young controls)		Crude OR	**11.00 (2.88; 41.99)**
	Malabsorbers vs. none (all controls)		Crude OR	**4.69 (1.45; 15.20)**
Kudlacek, 2002[92] Country: Austria Adults	Moderate lactose malabsorption vs. none	All fractures	Crude mean difference	0.24 (-0.03; 0.51)
		Vertebral fractures/patient		-0.17 (-0.34; 0.00)
	Severe lactose malabsorption	All fractures		**0.25 (0.02; 0.48)**

Table 12. Association between lactose intolerance or malabsorption and bone fractures (continued)

Study	Comparison	Outcome	Estimate	Mean (95% CI)
Ca++ intake difference in comparison groups: NR/NR	vs. none	Vertebral fractures/patient		**0.30 (0.03; 0.57)**
	Severe lactose malabsorption vs. moderate	All fractures		0.01 (-0.31; 0.33)
		Vertebral fractures/patient		0.47(0.20;0.74)
	Lactose malabsorption vs. none	Overall fractures	Crude OR	**2.63 (1.52; 4.54)**
	Moderate lactose malabsorption vs. none	Vertebral fracture per individual		**0.28 (0.09; 0.87)**
	Severe lactose malabsorption vs. none	Verterbral fracture per individual		**3.62 (1.93; 6.79)**
	Severe lactose malabsorption vs. moderate	Verterbral fracture per individual		**12.77 (4.12; 39.57)**
Harma, 1988[170] Country: Finland Elderly women Ca++ intake difference in comparison groups: NR/NR	LM (positive blood glucose test) vs. none	Spinal fracture	Age and sex matching OR	0.80 (0.18; 3.55)
	LM (positive blood glucose test) vs. none	Hip fracture		1.60 (0.50; 5.13)

Bold = statistically significant

Table 13. Association between low lactose diets, lactose intolerance or malabsorption, and osteoporosis

Study	Comparison	Outcome	Estimate	Mean (95% CI)
Osteopenia				
Country: Italy Adults	absorption	Lumbar		**5.63 (1.52; 20.86)**
		Femoral neck		**3.41 (1.03; 11.28)**
	symptoms vs. absorbers	Lumbar		**10.59 (2.66; 42.20)**
		Femoral neck		**7.77 (2.20;27.44)**
	symptoms vs. absorbers	Lumbar		1.96 (0.37; 10.47)
		Femoral neck		0.44 (0.05; 4.16)
	symptoms vs. lactose malabsorption without symptoms	Lumbar		**5.41 (1.32; 22.21)**
		Femoral neck		**17.65 (2.10; 148.65)**
Country: Taiwan postmenopausal Taiwanese women	Long-term vegan vegetarian practice vs. non long-term vegan and nonvegan vegetarians	Lumbar spine	physical activity, calcium, protein, and kcal	1.70 (0.86; 3.38)
	Long-term vegan vegetarian practice vs. short -term vegan and nonvegan vegetarians	Femoral neck		**3.94 (1.21; 12.82)**
Osteoporosis				
Birge, 1967[94] Country: USA Adults 50 years or over	History of milk intolerance	Osteoporosis	Crude OR	**7.56 (1.30; 43.98)**
Country: Taiwan Adults	Milk intake > vs.<2times/week: women	Osteoporosis		2.32 (0.69; 7.80)
	Milk intake > vs.<2times/week: men			1.97 (0.65; 6.06)
Country: Finland Postmenopausal women	T/T vs. C/C	Osteoporosis		0.41 (0.14; 1.19)
	C/T vs. C/C			0.82 (0.29; 2.32)
	T/T vs. C/T			0.51 (0.22; 1.17)
Obermayer-Pietsch, 2007[69] Country: Austria Postmenopausal women	T/T vs. C/C	Osteoporosis	Crude OR	0.58 (0.14; 2.38)
Finkenstedt, 1986[168] Country: Austria Women	LI vs. none	Osteoporosis	Crude OR	**32.31 (6.97; 149.75)**
Birge, 1967[94] Country: USA Adults 50 years or over	Positive vs. negative lactose tolerance test	Osteoporosis	Crude OR	**24.43 (1.27; 469.52)**
Finkenstedt, 1986[168] Country: Austria Women	LM vs. none	Osteoporosis	Crude OR	**36.56 (8.02; 166.69)**
Corazza, 1995[169] Country: Italy postmenopausal women	LI (clinical diagnosis) vs. none	Osteoporosis	Crude OR	2.04 (0.71; 5.86)

Bold = statistically significant

Figure 7. Association between genetic polymorphism TT vs. C/C and positive tests for lactose malabsorption, crude odds ratios from two Austrian observational population based studies of genetic screening for osteoporosis[66,69]

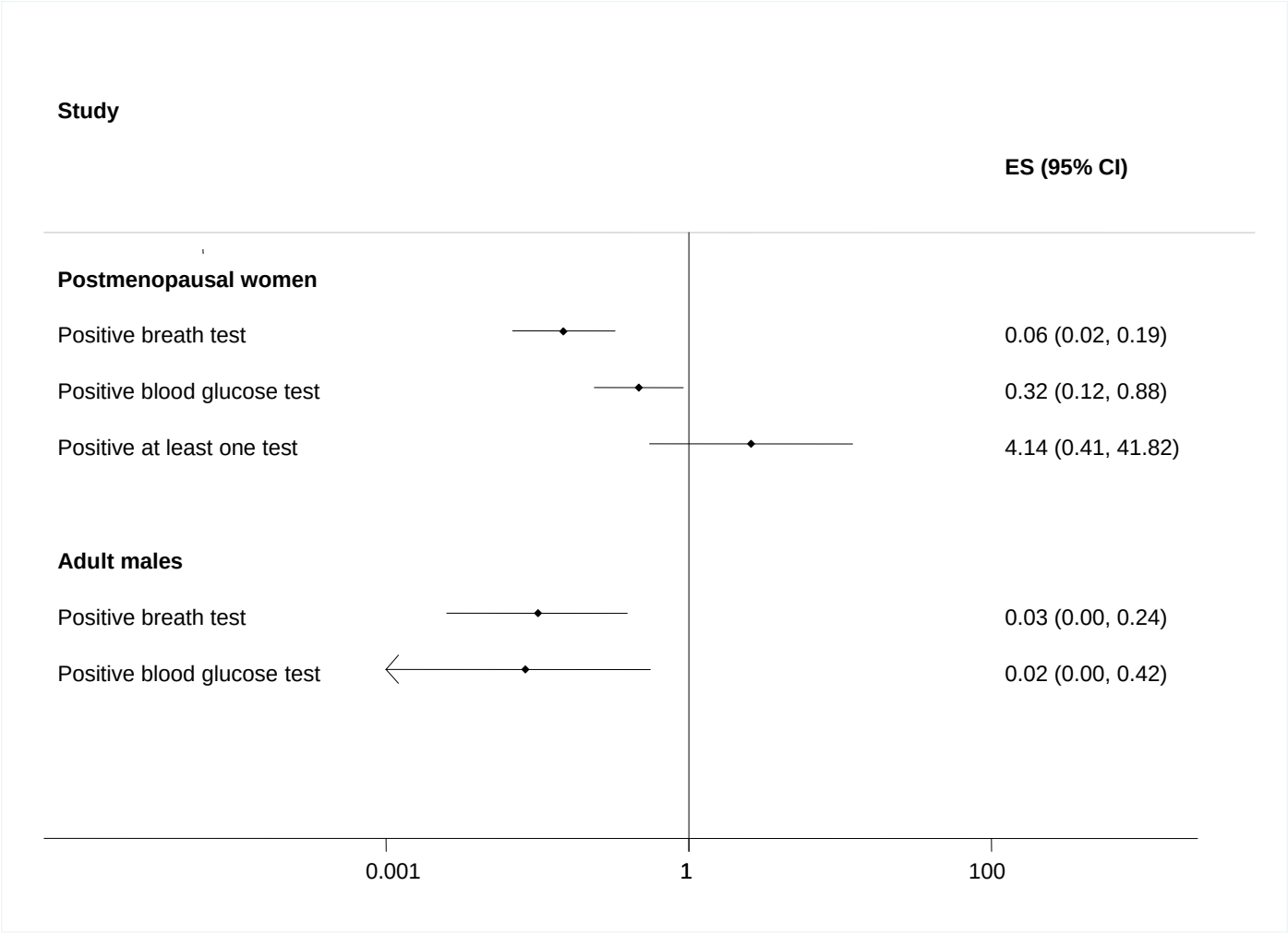


Table 14. Bone health outcomes in children and adolescents with low lactose diets (results from randomized controlled clinical trials of dairy products)

Skeletal Site	% Recommended Daily Values of Ca++ in Control Group with Low Lactose Diet / Months of Followup	Ca++mg/Day in Active vs. Control Group	Outcome Mean ± SD in Active Group	Outcome Mean ± SD In Control Group with Low Lactose Diet	Mean Difference (95% CI)
Bone Mineral Content (BMC)					
Total body BMC					
Chan, 1995[103] Country: USA Masking: Open label Sample: 48 Gender: 48 females Age: 11±1	56.0 / 12	1,068 vs. 463	1,695.00±317.00	1617.00±152.00	78.00 (-62.65; 218.65)
Cadogan, 1997[104] Country: UK Masking: Open label Sample: 82 Gender: 82 females Age: 12.2 years±3	54.1 / 18	1,125 vs. 703	428.00±88.00	391.00±107.00	37.00 (-5.41; 79.41)
Lau, 2004[101] Country: Hong Kong Masking: Open label Sample: 344 Gender: 181 males/143 females Age: 10.0 years±3	35.6 / 12	1,794 vs. 463	1,143.80±146.10	1,058.10±152.00	**85.70 (54.19; 117.21)**
	35.6 / 12	1,067 vs. 463	1,092.50±153.30	1,058.10±152.00	**34.40 (2.14; 66.66)**
	35.6 / 18	1,794 vs. 463	1,218.00±146.10	1,147.40±152.00	**70.60 (39.09; 102.11)**
	35.6 / 18	1,067 vs. 463	1,185.40±153.30	1,147.40±152.00	**38.00 (5.74; 70.26)**
Gibbons, 2004[102] Country: New Zealand Masking: The children were blinded to the study product Sample: 154 Gender: 75 males/79 females Age: 9.4 years±1	30.8 / 12	1,200 vs.400	1,394.00±23.00	1,383.00±29.00	**11.00 (2.73; 19.27)**
	30.8 / 18	1,200 vs.400	1,428.00±23.00	1,429.00±29.00	-1.00 (-9.27; 7.27)
Total hip BMC					
Lau, 2004[101] Country: Hong Kong Masking: Open label Sample: 344 Gender: 181 males/143 females Age: 10.0 years±3	35.6 / 12	1,794 vs. 463	17.50±3.07	16.10±2.64	**1.40 (0.80; 2.01)**
	35.6 / 12	1,067 vs. 463	16.60±2.46	16.10±2.64	0.50 (-0.04; 1.04)
	35.6 / 18	1,794 vs. 463	18.97±3.07	17.92±2.69	**1.05 (0.44; 1.66)**
	35.6 / 18	1,067 vs. 463	18.62±2.46	17.92±2.69	**0.70 (0.16; 1.25)**

Table 14. Bone health outcomes in children and adolescents with low lactose diets (results from randomized controlled clinical trials of dairy products) (continued)

Skeletal Site	% Recommended Daily Values of Ca++ in Control Group with Low Lactose Diet / Months of Followup	Ca++mg/Day in Active vs. Control Group	Outcome Mean ± SD in Active Group	Outcome Mean ± SD In Control Group with Low Lactose Diet	Mean Difference (95% CI)
Gibbons, 2004[102] Country: New Zealand Masking: The children were blinded to the study product Sample: 154 Gender: 75 males/79 females Age: 9.4 years±1	30.8 / 12	1,200 vs.400	19.10±0.40	19.00±0.50	0.10 (-0.04; 0.24)
Total femur BMC					
Cheng, 2005[107] Country: Finland Masking: DB Sample: 195 Gender: 196 females Age: 11.3 years±7	51.6 / 24	1,680 vs.671	25.90±3.20	26.20±3.90	-0.30 (-1.30; 0.70)
Femoral shaft BMC					
Bonjour, 1997[105] Country: Switzerland Masking: DB Sample: 149 Gender: 149 females Age: 7.9 years±06	87.9 / 12	1,723 vs.879	0.89±0.06	0.65±0.07	**0.24 (0.22; 0.26)**
	74.7 / 12	1,607 vs. 747	4.50±2.20	4.00±0.21	**0.50 (0.10; 0.90)**
Femoral neck BMC					
Lau, 2004[101] Country: Hong Kong Masking: Open label Sample: 344 Gender: 181 males/143 females Age: 10.0 years±3	35.6 / 12	1,794 vs. 463	1.81±0.27	1.71±0.26	**0.10 (0.04; 0.16)**
	35.6 / 12	1,067 vs. 463	1.76±0.27	1.71±0.26	0.05 (-0.01; 0.11)
	35.6 / 18	1,794 vs. 463	1.92±0.27	1.81±0.26	**0.11 (0.05; 0.17)**
	35.6 / 18	1,067 vs. 463	1.85±0.27	1.81±0.26	0.04 (-0.02; 0.10)
Chevalley, 2005[106] Country: Switzerland Masking: DB Sample: 235 Gender: 235 males Age: 7.4 years±4	74.7 / 12	1,607 vs. 747	1.59±0.18	1.64±0.22	-0.05 (-0.10; 0.00)

Table 14. Bone health outcomes in children and adolescents with low lactose diets (results from randomized controlled clinical trials of dairy products) (continued)

Skeletal Site	% Recommended Daily Values of Ca++ in Control Group with Low Lactose Diet / Months of Followup	Ca++mg/Day in Active vs. Control Group	Outcome Mean ± SD in Active Group	Outcome Mean ± SD In Control Group with Low Lactose Diet	Mean Difference (95% CI)
Cheng, 2005[107] Country: Finland Masking: DB Sample: 195 Gender: 196 females Age: 11.3 years±7	51.6 / 24	1,680 vs.671	3.99±0.40	3.95±0.05	0.04 (-0.04; 0.12)
Lumbar spine BMC					
Bonjour, 1997[105] Country: Switzerland Masking: DB Sample: 149 Gender: 149 females Age: 7.9 years±0.6	87.9 / 12	1,723 vs.879	1.78±0.20	1.30±0.18	**0.48 (0.42; 0.54)**
Lau, 2004[101] Country: Hong Kong Masking: Open label Sample: 344 Gender: 181 males/143 females Age: 10.0 years±3	35.6 / 12	1,794 vs. 463	27.47±4.06	26.29±4.13	**1.18 (0.31; 2.05)**
	35.6 / 12	1,067 vs. 463	27.71±5.07	26.29±4.13	**1.42 (0.44; 2.40)**
	35.6 / 18	1,794 vs. 463	31.65±4.06	28.81±4.13	**2.84 (1.97; 3.71)**
	35.6 / 18	1,067 vs. 463	30.60±5.07	28.81±4.13	**1.79 (0.81; 2.77)**
Gibbons, 2004[102] Country: New Zealand Masking: The children were blinded to the study product Sample: 154 Gender: 75 Males/79 Females Age: 9.4 years±1	30.8 / 12	1,200 vs.400	28.80±1.00	27.40±1.00	**1.40 (1.08; 1.72)**
	30.8 / 18	1,200 vs.400	28.50±1.00	28.80±1.00	-0.30 (-0.62; 0.02)
Chevalley, 2005[106] Country: Switzerland Masking: DB Sample: 235 Gender: 235 males Age: 7.4 years±4	74.7 / 12	1,607 vs. 747	1.97±0.80	1.99±0.81	-0.02 (-0.23; 0.19)
Cheng, 2005[107] Country: Finland Masking: DB Sample: 195 Gender: 196 females Age: 11.3 years±7	51.6 / 24	1,680 vs.671	34.20±5.60	34.00±5.60	0.20 (-1.37; 1.77)

Table 14. Bone health outcomes in children and adolescents with low lactose diets (results from randomized controlled clinical trials of dairy products) (continued)

Skeletal Site	% Recommended Daily Values of Ca++ in Control Group with Low Lactose Diet / Months of Followup	Ca++mg/Day in Active vs. Control Group	Outcome Mean ± SD in Active Group	Outcome Mean ± SD In Control Group with Low Lactose Diet	Mean Difference (95% CI)
Bone Mineral Density (BMD)					
Femoral trochanter BMD					
Bonjour, 1997[105] Country: Switzerland Masking: DB Sample: 149 Gender: 149 females Age: 7.9 years±0.6	87.9 / 12	1,726 vs.879	530.00±59.33	514.00±58.24	16.00 (-2.88; 34.88)
Femoral neck	**BMD**				
Bonjour, 1997[105] Country: Switzerland Masking: DB Sample: 149 Gender: 149 females Age: 7.9 years±0.6	67.6 / 12	1,725 vs.879	656.00±81.58	635.00±65.52	21.00 (-2.76; 44.76)
Femoral diaphysis	**BMD**				
Bonjour, 1997[105] Country: Switzerland Masking: DB Sample: 149 Gender: 149 females Age: 7.9 years±0.6	87.9 / 12	1,727 vs.879	1098.00±96.41	1077.00±87.36	21.00 (-8.54; 50.54)
Lumbar spine	**BMD**				
Chan, 1995[103] Country: USA Masking: Open label Sample: 48 Gender: 48 females Age: 11±1	56.0 / 12	1,069 vs. 463	0.77±0.09	0.75±0.08	0.02 (-0.02; 0.07)

Bold- statistically significant difference at 95% confidence level

Figure 8. Bone mineral content from RCTs of dairy product use in children and adolescents with low lactose diets. Total body

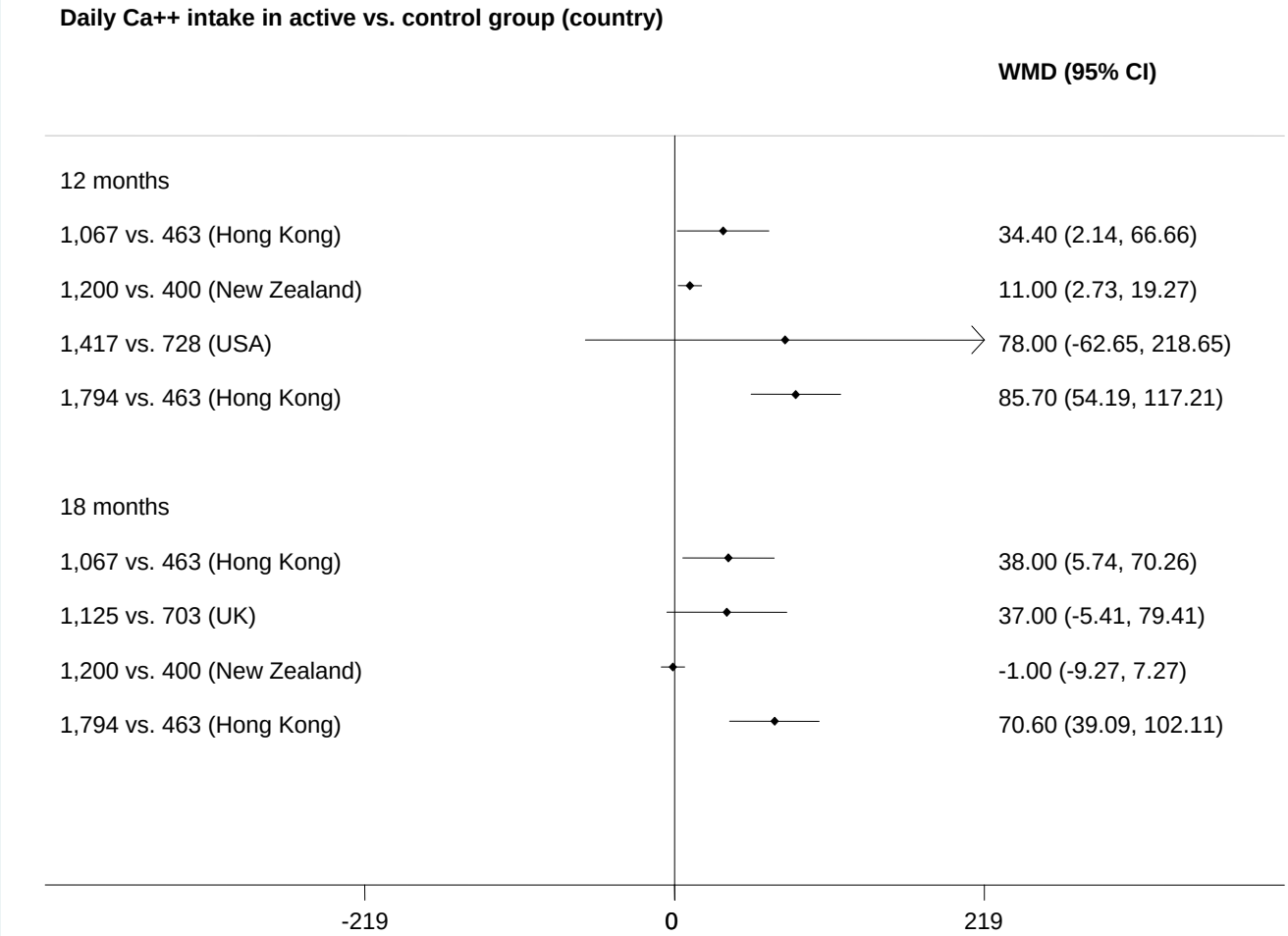


Figure 9. Bone mineral content from RCTs of dairy product use in children and adolescents with low lactose diets. Femoral neck

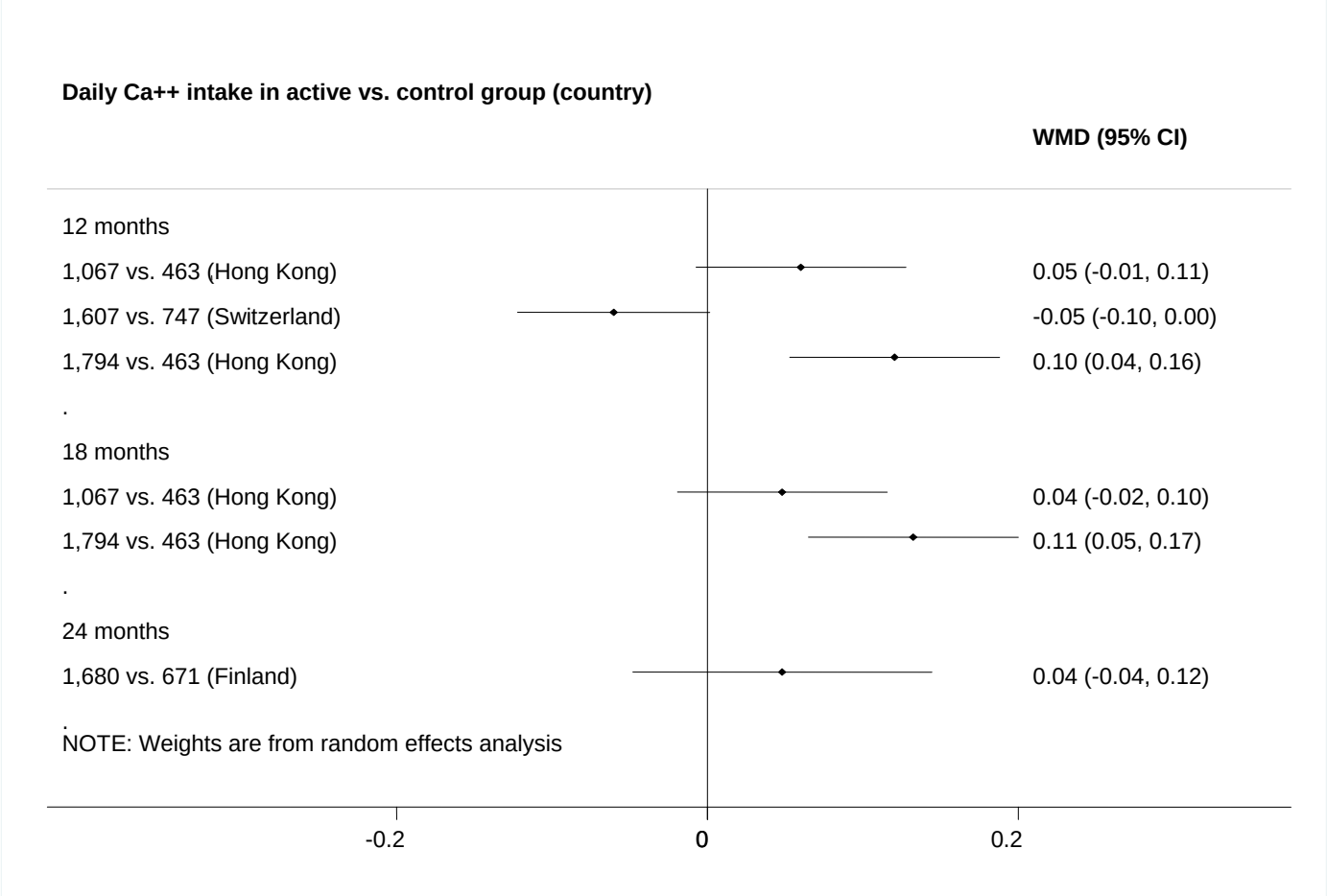


Figure 10. Bone mineral content from RCTs of dairy product use in children and adolescents with low lactose diets. Total hip

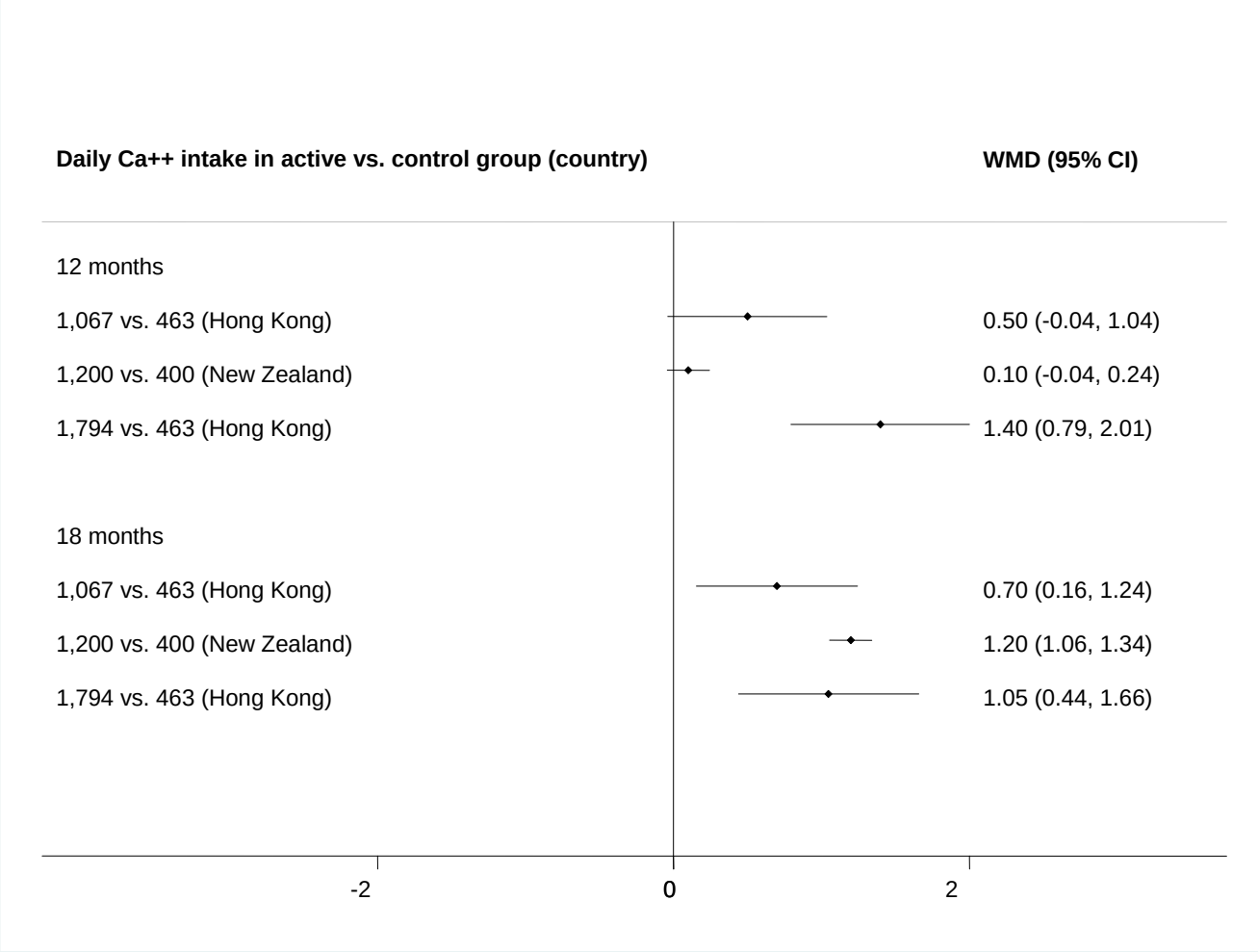


Figure 11. Bone mineral content from RCTs of dairy product use in children and adolescents with low lactose diets. Lumbar spine

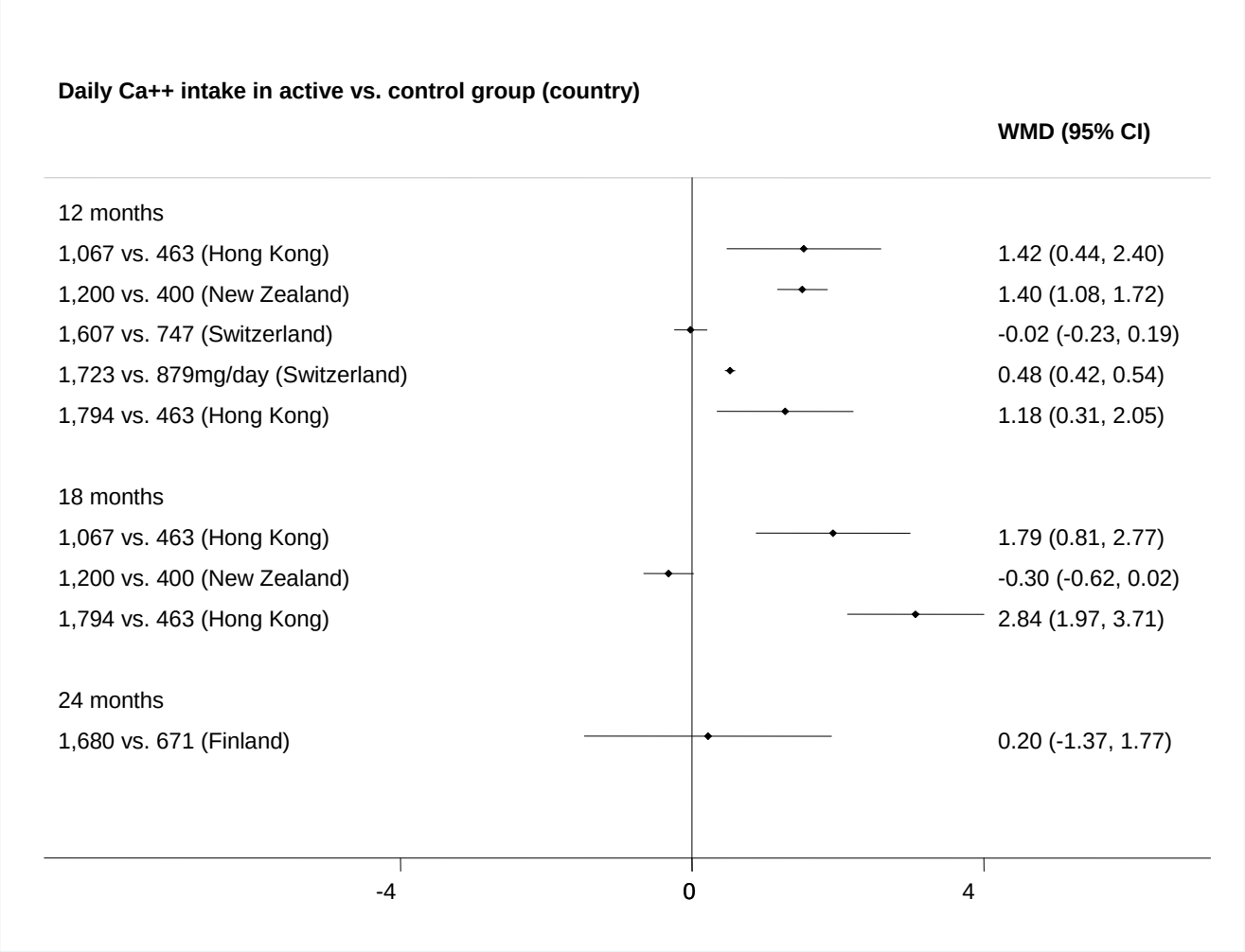


Table 15. Percent change in osteodensitometric values after administration of dairy products in children consuming low lactose diets (RCTs)

Study Sample	Outcome	Active, Mean STD	Control, Mean STD	Mean Difference (95% CI)
Gibbons, 2004[102] 74	Bone mineral density, total body	9.40±8.60	8.90±9.84	0.50 (-2.41; 3.41)
	Bone mineral density, lumbar spine	16.30±16.34	16.80±18.78	-0.50 (-6.05; 5.05)
	Bone mineral density, hip	14.00±16.34	12.40±17.89	1.60 (-3.81; 7.01)
	Bone mineral density, Trochanter	15.80±18.93	14.90±19.68	0.90 (-5.20; 7.00)
	Bone mineral density, femoral neck	15.40±16.34	15.30±15.21	0.10 (-4.90; 5.10)
	Lumbar spine L1-L4 volumetric density	54.30±55.92	60.50±65.29	-6.20 (-25.36; 12.96)
Cadogan, 1997[104] 44	Bone mineral density, lumbar spine	17.90±6.80	16.20±6.70	1.70 (-1.23; 4.63)
Cheng, 2005[107] 48	Bone mineral density	38.10±1.40	35.00±1.40	**3.10 (2.54; 3.66)**
	Bone mineral density in femoral neck (g)	26.50±1.40	22.40±1.50	**4.10 (3.52; 4.68)**
	Bone mineral content total femur (g)	36.90±1.60	33.60±1.60	**3.30 (2.66; 3.94)**
	Bone mineral density, spine L2-4 (g)	52.40±2.20	47.00±2.20	**5.40 (4.52; 6.28)**
	Bone cross-sectional area, radius (mm2)	26.20±2.00	21.30±2.00	**4.90 (4.10; 5.70)**
	Bone mineral content radius (mg/mm)	25.90±1.90	22.20±2.00	**3.70 (2.92; 4.48)**
	Volumetric bone mineral density, radius (mg/cm3)	3.07±1.50	1.99±1.50	**1.08 (0.48; 1.68)**
	Bone mineral density, tibia (mg/mm)	25.20±1.00	22.70±1.00	**2.50 (2.10; 2.90)**
	Volumetric bone mineral density, tibia (mg/cm3)	8.30±0.60	7.76±0.60	**0.54 (0.30; 0.78)**
Lau, 2004[101] 100	Bone mineral content, total hip	24.42±11.40	22.77±11.60	1.65 (-1.39; 4.69)
	Bone mineral density, total hip	7.28±4.10	6.34±4.20	0.94 (-0.16; 2.04)
	Bone mineral content, femoral neck	10.01±11.40	10.64±12.04	-0.63 (-3.72; 2.46)
	Bone mineral density, femoral neck	6.16±4.60	5.40±4.75	0.76 (-0.47; 1.99)
	Bone mineral content, spine	20.88±9.40	19.23±9.39	1.65 (-0.83; 4.13)
	Bone mineral density, spine	8.05±5.20	7.01±5.30	1.04 (-0.35; 2.43)
	Bone mineral content, total body	17.02±6.50	16.88±6.63	0.14 (-1.59; 1.87)
	Bone mineral density, total body	3.06±2.60	2.39±2.65	0.67 (-0.02; 1.36)
	Bone mineral content, total hip	25.89±12.02	22.77±11.60	**3.12 (0.01; 6.23)**
	Bone mineral density, total hip	7.41±4.24	6.34±4.20	1.07 (-0.04; 2.18)
	Bone mineral content, femoral neck	13.16±12.22	10.64±12.04	2.52 (-0.67; 5.71)
	Bone mineral density, femoral neck	6.48±4.95	5.40±4.75	1.08 (-0.20; 2.36)
	Bone mineral content, spine	21.51±9.70	19.23±9.39	2.28 (-0.23; 4.79)
	Bone mineral density, spine	8.37±5.45	7.01±5.30	1.36 (-0.06; 2.78)
	Bone mineral content, total body	18.46±6.77	16.88±6.63	1.58 (-0.18; 3.34)
	Bone mineral density, total body	2.87±2.73	2.39±2.65	0.48 (-0.23; 1.19)

Bold- statistically significant differences at 95% confidence level

Table 16. Association between lactose intake and metabolism and BMC

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Low lactose diets				
Vatanparast, 2005[160] Country: Canada Children and adolescents Ca++ intake difference in comparison groups: NR/NR	Calcium intake by mg/d, increment 1mg/day	Total-body BMC in boys	Adjusted for height, body mass, physical activity, intake of calcium, and intake of vegetables and fruit	**0.02 (0.00; 0.03)**
	Calcium intake by mg/d, increment 1mg/day	Total-body BMC in girls		NS
Parsons, 1997[95] Country: The Netherlands Adolescents Ca++ intake difference in comparison groups: -488/Y	Vegan type diet vs. regular diet in girls	BMC, total body	Adjusted for bone area, weight, height, percent body lean, age, and puberty	**-2.54 (-4.58; -0.50)**
	Vegan type diet vs. regular diet in boys	BMC, Total body		**-3.42 (-5.58; -1.26)**
		BMC, Spine L1–L4		**-8.53 (-12.98; -4.08)**
		BMC, Femoral neck		**-8.00 (-13.45; -2.55)**
		BMC, Trochanter		-3.54 (-9.69; 2.61)
		BMC, Radius 33%		**-6.79 (-10.24; -3.34)**
	Vegan type diet vs. regular diet in girls	BMC, Spine L1–L4		**-4.97 (-9.28; -0.66)**
		BMC, Femoral neck		**-8.15 (-12.80; -3.50)**
		BMC, Trochanter		**-5.84 (-10.62; -1.06)**
		BMC, Radius 33%		**-5.55 (-8.76; -2.34)**
Rockell, 2005[97] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: 182/Y	Milk avoiders, at 2 years of followup vs. baseline	Total body BMC (g)	Crude	**235.00 (216.00; 273.00)**
	Baseline vs. reference population	Total body BMC (kg)		**-0.44 (-0.76; -0.12)**
	At 2 years of followup vs. reference population	Total body BMC (kg)	Age adjusted	-0.19 (-0.50; 0.12)
	Baseline vs. reference population	UD radius BMC	Crude	**-0.30 (-0.57; -0.03)**
		33% radius BMC		-0.27 (-0.61; 0.07)
		Lumbar spine (L2–4) BMC		-0.16 (-0.43; 0.11)
		Femoral neck BMC		**-0.59 (-1.04; -0.14)**
		Hip trochanter BMC		-0.68 (-1.43; 0.07)
	At 2 years of followup vs. reference population	UD radius BMC	Age adjusted	**-0.31 (-0.58; -0.04)**
		33% radius BMC		-0.05 (-0.34; 0.24)
		Lumbar spine (L2–4) BMC		0.02 (-0.25; 0.29)
		Femoral neck BMC		0.08 (-0.22; 0.38)
		Hip trochanter BMC		**0.58 (0.28; 0.88)**
Black, 2002[76] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Age adjusted z scores in milk avoiders vs. reference healthy children	Total-body BMC (g)	Age adjusted	-0.45 (-0.90; 0.00)

Table 16. Association between lactose intake and metabolism and BMC (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Du, 2002[96] Country: China Adolescent Girls Ca++ intake difference in comparison groups: NR/NR	Increase in milk intake by 1 g/day	BMC at distal one-third ulna	Adjusted for physical activity, body weight, age, and socio-economic status regression coefficient	**0.0002 (0.0001; 0.0003)**
		BMC at distal one-third radius		**0.0003 (0.0002; 0.0004)**
		BMC at distal one-tenth ulna		**0.0003 (0.0002; 0.0004)**
		BMC at distal one-tenth radius		**0.0004 (0.0002; 0.0006)**
	No milk consumers vs. Low milk group (<22±18 g/day)	BMC (g/cm); distal one-third radius	Crude	-0.03 (-0.06; 0.00)
		BMC (g/cm); distal one-third ulna		0.00 (-0.03; 0.02)
		BMC (g/cm); distal one-tenth radius		**-0.07 (-0.12; -0.02)**
		BMC (g/cm); distal one-tenth ulna		-0.03 (-0.05; 0.00)
	No milk consumers vs. High milk group (>128±165 g/day)	BMC (g/cm); distal one-third radius	Crude	-0.02 (-0.05; 0.01)
		BMC (g/cm); distal one-third ulna		-0.01 (-0.03; 0.02)
		BMC (g/cm); distal one-tenth radius		-0.04 (-0.08; 0.00)
		BMC (g/cm); distal one-tenth ulna		-0.02 (-0.05; 0.00)
	Low milk group (<22±18 g/day) vs. High milk group (>128±165 g/day)	BMC (g/cm); distal one-third radius	Crude	0.00 (-0.03; 0.04)
		BMC (g/cm); distal one-third ulna		0.00 (-0.03; 0.02)
		BMC (g/cm); distal one-tenth radius		0.02 (-0.03; 0.08)
		BMC (g/cm); distal one-tenth ulna		0.00 (-0.03; 0.03)
Genetic polymorphism				
Enattah, 2004[57] Country: Finland Young men Ca++ intake difference in comparison groups: NR/NR	T/T vs. C/C	Lumbar spine BMC (g)	Crude	2.10 (-44.69; 48.89)
		Femoral neck BMC (g)		0.00 (-3.75; 3.75)
		Trochanter BMC (g)		0.10 (-15.18; 15.38)
		Total hip BMC (g)		2.40 (-25.98; 30.78)
	C/T vs. C/C	Lumbar spine BMC (g)	Crude	1.20 (-42.87; 45.27)
		Femoral neck BMC (g)		-0.20 (-4.26; 3.86)
		Trochanter BMC (g)		-0.10 (-14.97; 14.77)

Table 16. Association between lactose intake and metabolism and BMC (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
		Total hip BMC (g)		0.50 (-28.80;2 9.80)
	T/T vs. C/T	Lumbar spine BMC (g)	Crude	0.90 (-40.78; 42.58)
		Femoral neck BMC (g)		0.20 (-4.05; 4.45)
		Trochanter BMC (g)		0.20 (-14.23; 14.63)
		Total hip BMC (g)		1.90 (-23.08; 26.88)
Lactose intolerance				
Stallings, 1994[98] Country: USA Prepubertal children Ca++ intake difference in comparison groups: -383/Y	Lactose intolerance vs. none	BMC, g/cm adjusted for body size in LI subjects	Crude regression coefficient	**0.00006 (0.00001; 0.00011)**
	Lactose intolerance vs. none	BMC, g/cm	Crude	-0.01 (-0.08; 0.05)
Di Stefano, 2002[5] Country: Italy Adults Ca++ intake difference in comparison groups: -240/Y	Lactose intolerance vs. none	BMC (g): Lumbar spine	Crude	**-2.80 (-5.42; -0.18)**
	Lactose intolerance vs. none	BMC (g): Femoral neck		**-1.60 (-2.11; -1.09)**
Matlik, 2007[99]Country: USA 10- to 13-Year-Old Female Adolescents Ca++ intake difference in comparison groups: 168/Y	Perceived Lactose intolerance vs. none	Total body BMC, g	Adjusted for location (California or Indiana), race/ethnic group (Asian, Hispanic, or non-Hispanic white), and age (years), BMI and Tanner score	-69.65 (-147.74; 8.45)
		Spine (L2–L4) BMC, g		**-2.52 (-4.39; -0.64)**
		Total hip BMC, g		**-**0.95 (-2.05; 0.15)
		Femoral neck BMC, g		-0.14 (-0.30; 0.02)
		Total body BMC, g	Crude	-95.00 (-214.68; 24.68)
		Spine (L2–L4) BMC, g		**-3.15 (-5.39; -0.91)**
		Total hip BMC, g		-1.17 (-2.77; 0.43)
		Femoral neck BMC, g		-0.17 (-0.39; 0.05)
Lactose malabsorption				
Di Stefano, 2002[5] Country: Italy Adults Ca++ intake difference in comparison groups: -54/Y	Lactose malabsorption vs. none	BMC (g): Lumbar spine	Crude	-0.50 (-2.11; 1.11)
		BMC (g): Femoral neck		0.00 (-0.39; 0.39)
Matlik, 2007[99] Country: USA 10- to 13-year-old female adolescents Ca++ intake difference in comparison groups: 9/N	Lactose malabsorption vs. none	Total body BMC, g,	adjusted for location, race/ethnic group, and age. Diet models were also adjusted for weight, , BMI and Tanner score	**30.88 (45.07; 106.82)**
		Spine (L2–L4) BMC, g		-0.12 (-1.94; 1.71)
		Total hip BMC, g		**0.21 (0.83; 1.26)**
		Femoral neck BMC, g		**0.08 (0.08; 0.23)**

Table 16. Association between lactose intake and metabolism and BMC (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
		Total body BMC, g	Crude	-98.00 (-209.82; 13.82)
		Spine (L2–L4) BMC, g		-0.79 (-2.94; 1.36)
		Total hip BMC, g		-0.95 (-2.37; 0.47)
		Femoral neck BMC, g		-0.18 (-0.38; 0.02)
Goulding, 1999[71] Country: New Zealand Middle age and older women Ca++ intake difference in comparison groups: NR/NR	Malabsorbers vs. absorbers at baseline	BMC, g/cm^2 ultradistal radius	Adjusted for age, body weight, menopausal status, calcium intake regression coefficient	0.02 (-0.04; 0.00)
		BMC, g/cm^2 33% radius		0.01 (-0.04; 0.02)
		BMC, g/cm^2 , L2-4		-0.04 (-0.05; 0.12)
		BMC, g/cm^2, neck of femur		0.02 (-0.08; 0.04)
		BMC, g/cm^2, trochanter		0.01(-0.08;0.06)
		BMC, g/cm^2		0.00 (-0.05; 0.04)
		Total body mineral content (g)		-59.60 (-67.50; 186.70)
	Malabsorbers vs. absorbers at baseline at 12 months of followup	BMC, g/cm^2 ultradistal radius		0.00230 (-0.00700; 0.00200)
		BMC, g/cm^2 33% radius		0.00180 (-0.00900; 0.00500)
		BMC, g/cm^2 , L2-4		0.00540 (-0.02300; 0.01300)
		BMC, g/cm^2, neck of femur		-0.00150 (-0.01400; 0.01700)
		BMC, g/cm^2, trochanter		-0.00320 (-0.01900; 0.02600)
		BMC, g/cm^2		0.00040 (-0.01000; 0.00900)

Bold – statistically significant

Table 17. Effect of increased dairy intake on bone health in young[62] and pre-menopausal[63] women consuming low lactose diets (results from individual RCTs)

Study	Outcome	Ca++mg/day in Active vs. Control Group	Outcome Mean ± STD in Active	Outcome Mean ± STD in Control	Comments
Woo, 2007[62] Country: China Masking: Open label Sample: 441 Gender: Female Age: 28±8	Outcome: BMD Total spine; % change from baseline	1,446 vs. 446 (45% of recommended daily values)	1.49±NR	1.20±NR	Total spine BMD was significantly higher at 6 months in the milk group using per protocol analysis; otherwise no significant differences between the milk and control groups for both intention-to-treat and per protocol analyses
	Outcome: BMD, Total hip; % change from baseline		0.25±NR	0.25±NR	
	Outcome: BMD, whole body; % change from baseline		0.60±NR	0.75±NR	
Baran, 1990[63] Country: USA Masking: Open label Sample: 59 Gender: Female Age: 35.7-37	Outcome: BMD, vertebral ; % change from baseline	962 vs.892 (89% of recommended daily values)	-0.40±0.90	-2.90±0.80	The vertebral bone density in women consuming increased calcium did not change over the 3-year period (p>0.05). In contrast, the vertebral bone density in the control women declined (P< 0.001) and was significantly lower than that in the supplemented group at 30 and 36 months.

Key Question 3: What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance?

Optimally, studies of this question would employ the following methodology.

1. A large, randomly recruited group of subjects with a wide range of age and ethnicity would be tested for lactose malabsorption (the assumption being that subjects who do not malabsorb lactose cannot be lactose intolerant).
2. The lactose malabsorbers would undergo double-blind testing with a maximal physiological dose of lactose (50 grams) or an identical placebo to identify which subjects had appreciably more symptoms with lactose than the placebo. This study would identify subjects for further study with lower, more physiological dosages of lactose.
3. Subjects with lactose intolerance would then be tested in double-blind fashion with a range of doses of lactose or identical placebo in an attempt to determine at what dosage lactose symptoms convert from tolerable to intolerable. To simulate a true life situation, the lactose would be administered with meals throughout the day. The subjects would provide a global assessment of their symptoms as well as a daily severity assessment of various symptoms on a numerical scale. The dose of lactose that induced a global rating of unacceptable ("intolerable"), or a significant increase in symptom score relative to the rating of the placebo, would be determined. The numerical scoring system would be converted to biological relevance, i.e., what difference in symptom score differentiates "tolerable" versus "intolerable."
4. Lastly, data would be analyzed to determine if the tolerable dose of lactose in malabsorbers is influenced by age and ethnicity.

Characteristics of Included Studies

Twenty-eight randomized (to treatment order), crossover, trials were included (Appendix Table D9).[108-115,117-135] Nearly all trials reported utilizing a double blinded approach, but three studies were single blinded or did not attempt to mask the tastes of the test preparations.[115,130,131] Trial populations ranged between six and 150 subjects. Women constituted 55 percent of the subjects (n=22 studies). The mean age of subjects was 37 years of age with a range between 10 and 77 (n=20 studies). Seven trials included children or adolescents, four exclusively.[109,114,120,123,126,127,135] One trial enrolled elderly subjects (mean age 77 years).[116] Within the 20 studies reporting race or ethnicity, 34 percent of subjects were white, 30 percent Hispanic, 20 percent black, 8 percent Asian, and 7 percent other.[109-116,118,120,123,126-131,133-135] One study was exclusively American Indians.[120] Fifteen studies were conducted in the United States,[109-111,113,114,116,118-120,125-127,130,131,135] eight in Europe,[108,112,121-124,132,134] three in Latin America,[128,129,133] one in Asia,[117] and one in Australia.[115] Sixteen studies utilized commercial lactase products or hydrolyzed milk,[108-111,113-115,121-125,128,130,133,135] two used milk products with lactose removed by ultrafiltration or chromatographically,[112,134] and three assessed nonlactose solutions.[116,126,127] An unclear or unreported method of lactose removal was noted in two trials.[129,132] One trial involved probiotics,[117] one was a colonic adaptation study,[118] and three trials assessed varying levels of daily lactose (added to water or in sugar packets to be added to breakfast).[119,120,131] In 11 studies, abdominal symptoms compatible with malabsorption of lactose prior to study entry were not required for study participation (based solely on biochemical diagnosis) or subjects were not reported to experience symptoms following ingestion of lactose.[115-117,120,122,126,127,129,130,133,135]

Lactose malabsorption was diagnosed following lactose tolerance tests by the hydrogen breath test in 13 of the studies,[108-120] and blood glucose test in 11 studies.[121-131] Diagnosis based on urinary galactose concentration was reported in one study[132] and biochemical method of diagnosis was not reported in three trials.[133-135] Half of the trials included lactose digesting controls.[110-113,116,120,122,125-129,133,135]

Overview of Findings

Existing studies do not fulfill the ideal criteria described above. The vast majority of studies of LI have been small (<30 subjects). While age and ethnicity of the subjects is often provided, tolerance to lactose of these subgroups of subjects has not been studied. While subjects are routinely tested for LM, only a few studies have then tested the intolerant subjects in blinded fashion with increasing doses of lactose administered throughout the day to determine the daily tolerable dosage of lactose. Most studies have utilized a single dose of lactose and a lactose free control administered in water or milk without food, frequently in not totally blinded fashion (i.e., the taste of low lactose milk differs from milk). The statistical rating of symptoms is rarely related to biological significance. The probability that a given dose of lactose induces more symptoms than the control treatment has been assessed by standard statistical tests of the differences between group means. No attention has been paid to the possibility of outliers, i.e., selected subjects who consistently might be particularly sensitive to lactose induced symptoms. In contrast to the massive amount of data on LM and ethnicity, published data do not allow one to determine if the daily tolerable dose of lactose in lactose malabsorbers differs by age and ethnicity. Thus, it can be stated, a priori, that it is not possible to provide reliable answers to many of the questions raised in this section of the report. Results were heterogeneous in terms of patient populations, interventions, assessment methods, and outcome definitions, thus precluding pooling. We provide a description of the individual studies and their results stratified by key study design characteristics of interest.

Experimental Studies of the Tolerance of Individual Subjects to Lactose

A wide variety of methodologies have been employed to assess the ability of subjects to tolerate lactose. The vast majority of studies initially dosed a group of volunteers with a high (30 grams to 50 grams) dose of lactose, and the subjects were classified as malabsorbers or absorbers based on breath H_2 measurements or blood glucose rise. In addition, the malabsorbing subjects were characterized as being lactose tolerant or intolerant based on the reporting of appreciable (variable from one study to the next) symptoms reported during this testing. A blinded control was virtually never employed during this portion of the study; thus, it is possible that some of the subjects categorized as lactose intolerant might have had similar symptoms following ingestion of a lactose free control solution.

In some studies only the lactose intolerant individuals were then tested in some sort of blinded fashion with a dosage or dosages of lactose, while in other studies both the lactose tolerant and the intolerant subjects were tested. The lactose free or lactose reduced milks that served as the controls usually were produced by prehydrolysis of milk with lactase, a process that produces a milk sweeter than that of conventional milk (glucose and galactose released from lactose is sweeter than lactose). Some studies did not blind for this taste difference, while other studies employed a

variety of methods to disguise this taste difference, including the addition of an artificial sweetener to milk, chocolate, and commercial lactose free dietary supplements. A sizable variability of the response of malabsorbers to the placebo was observed in various studies, ranging from nil in some studies to very appreciable in others. In addition, there was large inter-study variability in the response of the absorbers/lactose tolerant to the lactose containing or lactose free treatments. A striking example of the potential for nonlactose induced symptoms in this testing was provided by the study of Haverberg, et al.,[126] in which 32 percent of lactose absorbers reported symptoms after ingestion of 480 ml of lactose free milk. A further example of the potential importance for taste blinding was the study of Reasoner, et al.,[125] in which the addition of 0.2 percent glucose to milk reduced the symptomatic response to milk. Presumably this low concentration of glucose induced its effect via an influence of the taste of the milk rather than lactose digestion/absorption. Some studies have administered lactose (or low lactose controls) with meals, while most studies have employed a single dose of milk or control ingested without food (usually in the morning after arising). The former is more physiological, while the latter eliminated the confounding effect of other food on symptom response.

Studies Using a Range of Dosages of Lactose

The study of Hertzler and Savaiano[118] provided the literature's most optimistic appraisal of the daily dosage of lactose that is tolerable by lactose intolerant subjects. Eighteen healthy young adult subjects with self diagnosed LI were demonstrated to be lactose malabsorbers. In a randomized, double blind crossover study, subjects received either sucrose or lactose for a 10-day period with a 2-day washout between feeding of the opposite sugar. The initial daily dosage of the sugar (lactose or sucrose) was 42 grams in evenly divided doses with meals, and this dose was incrementally increased to 70 grams/day over the 10-day period. Comparison of the daily symptom records showed no statistically significant difference between the sucrose and lactose feeding periods for any dosage of the sugars. Thus, subjects had negligible symptoms at the initiation of lactose feeding (42 grams per day) and by the end of the 10-day period, were tolerating 70 grams (almost 1.5 quarts of milk) per day. If the results of this study of 18 self diagnosed lactose intolerant subjects could be extrapolated to the universe of lactose intolerant individuals, LI would not represent an appreciable clinical problem, provided lactose was routinely ingested in divided doses with meals. The investigators attributed the apparent extraordinary tolerance to lactose at the end of the feeding period to adaptation of the colonic flora towards bacteria that ferment lactose via nongas producing pathways. Lactose ingestion was associated with a nonsignificantly greater flatus and diarrhea severity score on virtually each of the 10 days of the study, and a statistical analysis of the sum of the 10-day records, if provided, may have demonstrated a significant (but small) increase in symptoms with lactose.

Stephenson et al.,[131] studied 14 healthy young adult subjects who were intolerant to a 50 gram dose of lactose. The subjects were then fed increasing dosages of lactose in water or in milk, with tolerance to lactose defined as two or less mild symptoms following lactose ingestion. All subjects tolerated the 15 gram dose, the vast majority tolerated 30 grams, while only 5/14 tolerated a 50 gram or greater dosage. Thus, 30 grams was the usual tolerable dose. Subjects were not blinded nor were the dosages of lactose randomly assigned.

Newcomer et. al.[120] randomly fed 59 Native American lactose malabsorbers (three children and 56 adults) dosages of lactose ranging from 0-18 grams with a sweet roll and 8 ounces of Ensure® to disguise the difference in tastes of the test meals. Any symptom greater than slight was

considered an appreciable problem. There was no significant correlation between the dosage of lactose and the frequency of appreciable symptoms up to a dosage of 18 grams of lactose. Jones, et al.[130] fed variable doses of lactose in the form of milk or lactose reduced milk with breakfast to 16 lactose malabsorbers. Symptoms were comparable for 7.5 grams and 15 grams lactose dosages, but a significant increase in symptoms was observed with 30 grams. In a second study in this paper (15 subjects) symptoms were similar for placebo and milks containing 10 grams of lactose; however, symptoms increased significantly ($p<0.05$) when lactose dosage was increased to 25 grams. No effort was made to disguise the taste of the milk. This study shows that up to 15 grams of milk is tolerated by an unselected group of lactose malabsorbers, whereas 25 (or 30 grams) yields a statistically significant increase in symptoms.

In a study by Cavalli-Sforza, et al.[122] 40 adult lactose malabsorbers were randomly fed four different doses of lactose, each test period lasting 4 days. Dosages were 125, 250, 500, and 1,000 ml/day of milk or lactose hydrolyzed milk. A significant positive correlation between increasing dosage and symptoms was observed with milk. The percentage of subjects reporting symptoms with the 125 ml, 250 ml, 500 ml, 1,000 ml dosages were about 30 percent, 45 percent, 55 percent, and 65 percent, respectively. The symptomatic response to low lactase milk was about 10 percent less at each dosage. Symptoms seldom were severe. This study suggests that the frequency of mild symptoms increases with increasing dosage of lactose over the range of 125 ml of milk (6 grams of lactose) to 1,000 ml of milk (50 grams of lactose), with no clear-cut threshold for tolerance versus intolerance. Given the sizable percentage reporting symptoms with lactose hydrolyzed milk, lactose was only partially responsible for this symptom response.

Hertzler et al.[119] fed 13 healthy adult lactose malabsorbers varying dosages of lactose (0 to 20 grams) in water without other food. Authors masked taste differences with aspartame. A statistically significant increase in symptoms was observed when the dose of lactose reached 20 grams, although mean symptom severity score was less than “slight.” Results suggest that the ability of lactose malabsorbers to ingest lactose without detectable symptoms occurs between a 12 gram and 20 gram dosage of lactose when the sugar is administered in water without other food.

Two studies of adolescents investigated the response to 240 and 480 ml of lactose-containing and lactose-free milk. Haverberg, et al.[126] studied 43 lactose absorbers and 67 malabsorbers where the flavors were disguised with chocolate. There was no significant difference in symptomatic response of malabsorbers and absorbers to the 240 ml (12 grams lactose) dose nor was the response of malabsorbers to the two types significantly different. These comparisons showed greater differences for the 480 ml dosages. It was calculated for the lactose malabsorbers that the lactose content of 240 ml and 480 ml of milk might have induced symptoms in 5 percent and 24 percent of the subjects, respectively. The majority of the symptoms reported after milk ingestion by these subjects (particularly with the 240 ml milk dosage) were caused by factors other than LI. Kwon et al.,[127] using similar methodology to that of Haverberg et al.,[126] studied 45 malabsorbers and 42 absorbers. With the 240 ml dosage of milk, a higher percentage of absorbers (19 percent) had symptoms with the lactose containing milk than did malabsorbers (9 percent). However, with 480 ml of milk, a greater percentage of malabsorbers (27 percent) had symptoms versus absorbers (17 percent) and a greater percentage of the lactose malabsorbers had symptoms with the lactose containing (27 percent) than with the lactose free milk (16 percent). Statistical significance was not computed. This study showed that lactose malabsorbers tolerate the lactose content (11 grams) of 240 ml of milk, but a percentage of these subjects (about 16 percent) apparently experience lactose induced symptoms from a 22 gram dose of lactose (480 ml of milk).

Lybeck-Sorenson et al.[134] tested 35 well nourished Latin American malabsorbers with 250 ml or 500 ml of lactose-containing and a low lactose milk from which 86 percent of the lactose had been removed. The products were said to be similar in taste and consistency. Doses of lactose fed (with a light breakfast) were 1.6 grams (250 ml, lactose- reduced milk), 3.2 grams (500 ml, lactose reduced milk), 11.3 grams (250 ml milk), 22.5 grams (500 ml milk), and 50 grams (lactose tolerance test). The respective median symptom scores for these lactose loads were 0.3, 0.2, 0.5, 1.1, and 6.1, with a maximal score of 12. No significant increase in symptoms was noted between conventional and low lactose milk at the 250 ml dosage, while a significant increase was noted with the 500 ml dosage, although symptoms tended to be slight (score 1.1 out of 12). When the lactose dosage was increased to 50 grams (1,000 ml of milk), symptoms became appreciable (score 6.1 out of 12), although there was no control for this phase of the study. This study demonstrates that 11.3 grams of lactose was tolerated, 22.5 grams yielded mild symptoms, and 50 grams was clearly intolerable.

Lisker et al.[129] studied 97 lactose malabsorbing, healthy adult Mexican subjects. The subjects received 250 ml of milks containing 0 grams, 12.5 grams, and 37.5 grams of lactose, with taste difference disguised with chocolate. Compared to the lactose free preparation, the 12.5 gram dose induced a highly significant increase in symptoms (16 percent were severe) and the 37.5 gram dose resulted in very severe symptoms in 71 percent of subjects. This is the only study using multiple dosages of lactose in which appreciable symptoms were observed with 12 grams of lactose.

Vesa et al.[112] tested 39 lactose malabsorbers with 250 ml of lactose free milk to which lactose was added in quantities of 0, 0.5, 1.5, and 7 grams. Symptoms were not significantly different for the various doses, showing that malabsorbers can tolerate small amounts of lactose (7 grams), such as might be used in coffee or cereal.

The above studies involving the feeding of incremental dosages of lactose to determine the amount of lactose tolerated by lactose intolerant subjects were all carried out with adult subjects, and no data were provided to correlate tolerance with age or ethnicity. All but one of the studies assessed tolerance to a single dose of lactose (frequently without food) and thus provided no data on the daily dosage of lactose that might be tolerated, assuming tolerance is improved if lactose intake is distributed throughout the day with meals. The one study that investigated symptoms when lactose was ingested for 1 week with each of the three meals showed that up to 70 grams of lactose/day could be tolerated without appreciable symptoms.[118] The results of single feeding studies generally demonstrated that a 12 gram dose of lactose (one cup of milk) produces negligible symptoms with intolerance occurring at dosage ranging between 20 and 50 grams of lactose.

Studies Comparing Symptoms Resulting from the Ingestion of One Dosage of Lactose Versus that of a Lactose Reduced or Lactose Free Treatment

Adult and adolescent studies: Evaluating daily dosage of approximately 12 grams of lactose (250 ml of milk). Suarez et al.[113] recruited 30 subjects who self reported extreme intolerance to milk. Nine of these subjects were demonstrated to be lactose absorbers via breath testing. This finding, which was observed in other studies, demonstrates the tendency of subjects to misdiagnose themselves as lactose intolerant. For 1-week periods, the lactose malabsorbers ingested 250 ml/day of conventional milk with their usual breakfast and during another week they receive 250/ml of lactose hydrolyzed milk, the taste difference masked with an artificial sweetener.

There were no statistically significant differences in symptoms (gas, flatulence, abdominal discomfort, bloating) between the two testing periods. A surprising finding of this study was that symptoms were trivial during both testing periods, despite the pre-study perception of the subjects that lactose induced severe symptoms.

The finding of negligible symptoms with 12 grams of lactose was also observed by Rorick et al.[116] in a study of 87 healthy elderly subjects (mean age 77). Either 240 ml of milk or 240 ml of lactose free milk (taste disguised with chocolate) was fed to 64 lactose absorbers and 23 lactose malabsorbers without food. The percentage of subjects with symptoms was similar (about 70 percent) for the absorbers and the malabsorbers. The percentage of subjects reporting symptoms to lactose-containing but not lactose-free milk (i.e., "lactose intolerance") was actually higher for the lactose absorbers versus the malabsorbers.

Paige et al.[135] studied 22 African American adolescent malabsorbers. Subjects received three 240 ml treatments: whole milk (12 grams of lactose), 50 percent lactose hydrolyzed milk (6 grams of lactose), and 90 percent lactose hydrolyzed milk (1.2 grams of lactose). Symptoms were reported by 3/22 subjects after ingestion of conventional milk, but two of these three subjects also had symptoms after ingestion of the 90 percent hydrolyzed milk. Thus, 1/22 subjects may have had symptoms attributable to LI.

In contrast, several groups have reported appreciable symptoms after ingestion of approximately 12 grams of lactose. Johnson, et al.[114] fed 315 ml of milk (about 15 grams of lactose) or lactose free milk (taste difference disguised with artificial sweetener) to 45 lactose malabsorbing, young adult African Americans. Symptoms were reported by 100 percent of subjects with the lactose containing milk; however, 33 percent had symptoms with lactose free milk as well. Thus, 67 percent of this group of African American subjects appeared to have symptoms attributable to lactose, although the severity of symptoms was not studied. Brand et al.[115] compared the symptomatic response of six lactose absorbers to conventional milk with that of lactose reduced milk with no blinding for taste differences. Five subjects had at least one symptom of flatulence, diarrhea, or cramps with conventional milks, whereas no subjects reported symptoms with 95 percent hydrolyzed milk. Symptom severity was recorded but not presented, other than that mild to moderate diarrhea was reported by three of the six subjects. Reasoner et al.[125] studied nine milk intolerant individuals (defined as responding to a 50 gram lactose challenge with a positive breath test and appreciable symptoms). While multiple milks were tested, the three types pertinent to this study were conventional skim milk, conventional skim milk with added glucose (0.2 percent), and low lactose milk (approximately 80 percent lactose hydrolyzed). Taste differences were not disguised. The average scores for pain and gas were statistically significantly higher ("moderate") for untreated skim milk versus the lactose hydrolyzed milk where symptoms were slight. No significant difference was observed for flatulence. Of interest, symptoms with the skim milk containing 0.2 percent glucose, added to simulate the taste of the hydrolyzed milk, induced less symptoms than did the skim milk. Although not analyzed statistically, differences between this milk and lactose hydrolyzed milk appeared to be insignificant.

Daily dosage of 18 to 25 grams of lactose (350 ml to 500 ml of milk). Suarez et al.[111] studied the symptoms of 32 lactose malabsorbers when they ingested 240 ml of milk or lactose free milk with breakfast and dinner for 1-week periods (24 grams of lactose daily x 7 days with lactose-containing milk). Differences in milk flavors were disguised with artificial sweetener. While each of the symptoms was scored higher during the lactose ingestion period, none of the difference reached statistical significance. Mean symptom scores for gas, bloating, abdominal pain, and diarrhea were trivial with both types of milk. Of interest, symptoms during both the 24 gram

lactose and the zero lactose test periods were significantly higher if, prior to testing, the subjects deemed themselves to be lactose intolerant.

Vesa et al.[132] studied 30 Estonian malabsorbers. Subjects ingested 200 ml of conventional or lactose free milk twice daily (with breakfast and before lunch) for 2-day test periods (about 20 grams of lactose daily). No significant differences in symptoms were observed between the periods when subjects ingested lactose-containing versus lactose free milk.

Lin et al.[117] fed 400 ml of milk (20 grams of lactose) to 20 healthy malabsorbers with a placebo or one of four different commercial beta-galactosidase preparations. The numerical ratings of symptoms of gas, "stomach" pain, and diarrhea were significantly less when each of the beta-galactosidase preparations was ingested with milk compared to milk ingested with placebo. However, the symptoms seemingly were relatively minor with a severity score, out of a maximum of 40, being 7.85 for gas and only 1.55 and 1.20 for "stomach pain" and diarrhea, respectively.

Montalto et al.[108] studied 30 lactose malabsorbers who ingested 400 ml of milk (about 20 grams of lactose). The treatments consisted of conventional milk, milk pretreated with lactase, and milk taken 5 minutes after ingestion of a commercial beta-galactosidase preparation. The treatments were not blinded. Symptoms were significantly ($p<0.001$) higher for tests in which the milk was ingested without pretreatment with lactase. The mean overall symptom severity score when conventional milk was ingested without lactase was about 4, apparently out of a maximum of 12.

Rosado et al.[133] studied 25 Mexican malabsorbers who ingested 360 ml of milk (18 grams of lactose) with and without pretreatment of the milk with a commercial beta-galactosidase. The study was not blinded. Symptoms were observed in 12 of 25 subjects with untreated milk and four of 12 with enzyme treated milk, and the median symptom grade in the 12 subjects ingesting untreated milk was "major." A sizable reduction ($p<0.01$, paired t test) was observed in severity score with beta-galactosidase treated milk.

Rask Pedersen et al.[124] studied 11 Danes with lactose malabsorption. Subjects received 500 ml of milk (25 grams of lactose) or lactose hydrolyzed milk without other food, apparently with no blinding for taste differences. Symptoms of diarrhea and flatulence were severe in 5/12 with milk and only 1/12 with lactose hydrolyzed milk, and statistical analysis showed the reduction in symptoms was significant ($p<0.02$).

Summary of results with 18-25 grams of lactose. The results of studies performed with 18 to 25 grams of lactose ranged from excellent tolerance by malabsorbers[111,132] to a high frequency of appreciable intolerance symptoms.[108,124,133] The two studies[111,132] in which tolerance was observed supplied lactose in divided doses with meals, while studies that showed appreciable intolerance supplied lactose as a single dose without food. These few observations suggest that a daily dose of 18 to 25 grams of lactose may be tolerable to lactose malabsorbers if lactose intake is distributed throughout the day with meals.

Lactose dosage greater than 25 grams/day. Suarez et al[110] enrolled 62 women, 31 lactose absorbers and 31 lactose malabsorbers, in a study to determine the tolerance to a diet that supplied 1,300 mg of calcium per day in the form of dairy products. To this end, for 1-week periods, each day the subjects ingested 480 ml of milk (240 ml at breakfast, 240 ml at dinner), 240 ml of yogurt at lunch, and 56 grams of hard cheese. One week the subjects ingested conventional products that had a total lactose content of 34 grams, and in another week the lactose in the milk and yogurt prehydrolyzed via treatment with beta-galactosidase (this diet contained 2 grams of lactose per day). Subjects rated symptoms twice daily on a zero to five scale. Perception of rectal gas, frequency of gas passages, bloating, and frequency of bowel movements all were significantly (p

<0.05) greater when the lactose malabsorbers ingested the lactose rich diet. However, the mean symptom score seldom exceeded “slight.” No significant differences were observed between the two treatment weeks by the lactose absorbers. Despite the higher symptom severity scores recorded during the high lactose week, when queried as to the week they perceived their symptoms were greater, 15 identified the high lactose week, eight the low lactose week, and eight noted no difference ($p = 0.21$). Two-thirds of the malabsorbers felt that the symptoms during the high lactose week were less severe than they anticipated. A roughly equal percentage (about 50 percent) of lactose absorbers and malabsorbers indicated a willingness to obtain their calcium via the lactose rich diet, and conversely about 50 percent in each group indicated that they would prefer to obtain their daily calcium requirement via ingestion of calcium tablets. This study suggests that if dairy products are supplied as two cups of milk (distributed throughout the day), yogurt, and hard cheese, LI is not a major impediment to the daily ingestion of 34 grams of lactose.

Cheng et al.[128] studied 15 Chilean penitentiary inmates who were lactose malabsorbers. For 30 days the subjects ingested a baseline diet which included 500 ml of low lactose milk taken twice daily at 8:30 am and 4:30 pm. On three occasions on weeks 2, 3, and 4 of this regimen, conventional milk sweetened with 5 percent sucrose was substituted for the low lactose milk. A marked increase in the frequency and severity of abdominal pain, diarrhea, distension, and flatulence ($p < 0.001$ for each symptom) was observed on the days that conventional milk was substituted for the low lactose milk. No such increase in symptoms was observed in lactose absorbers. Although probably not perfectly blinded, this study indicated that in subjects ingesting a diet low in lactose, 50 grams of lactose in two divided doses during the day yields severe intolerance symptoms.

Xeno et al.[121] dosed lactose malabsorbers with 100 grams of lactose in water, with a placebo or tablet, or a tablet containing beta-galactosidase. Symptoms were rated on a zero to four scale. While symptoms appeared to be more severe during the placebo phase of the study, no statistical analysis of the results was performed. Severe symptoms with the placebo were reported for abdominal cramping (3/8), bloating (1/8), flatulence (2/8), and diarrhea (2/8), and 2/8 reported vomiting. No severe symptoms were reported when beta-galctosidase was ingested. While the marked intolerance to 100 grams of lactose taken as a single dose was not unexpected, this study was unique in its use of such a large dose of lactose.

The studies testing the tolerance of lactose malabsorbing subjects to a single dose of lactose yielded discordant results. Multiple studies showed no appreciable increase in symptoms with the 12 gram dose, while others showed appreciable symptoms. The explanation for this discrepancy is not clear. When the dosage of lactose was increased to 18 to 25 grams, once again, the finding of intolerance varied between studies. However, the difference in tolerance observed in these studies could be explained by the better tolerance of lactose if the ingestion of this sugar was distributed throughout the day as opposed to ingestion of lactose as a single dose without food.

Studies in children. The tolerance of children to a given dose of lactose might differ from that of adults because of differing physiology in children and/or the greater dosage/kg of body weight.

Gremse et al.[109] studied the effect of lactose on unexplained abdominal pain in 30 children (mean age 11.4 ± 2.5) lactose malabsorbers. The subjects were provided with 250 ml of regular or lactose hydrolyzed milk (taste disguised with artificial sweetener) for 2-week periods. Their abdominal pain scores increased from 4.1 on lactose free milk to 7.5 on lactose containing milk, a difference with a p value of 0. 021. No significant differences were observed for flatulence, diarrhea, or bloating. The mean pain score observed with milk (7.5) appeared to be trivial, given a maximal possible score of 54. Only 5/30 subjects appear to have had an appreciable increase in

pain with introduction of lactose, and four of these subjects had the highest pain scores on the lactose free diet. Thus, the pain of these subjects was aggravated, but not solely caused, by lactose.

Nielsen et al,[123] studied the tolerance of nine lactose malabsorbing children (mean age 10, range 9-16) via the feeding of 500 ml of conventional or lactose hydrolyzed milk, with no effort to disguise taste differences. Symptoms of abdominal pain, flatulence, and diarrhea were very significantly greater after ingestion of the nonhydrolyzed milk. Thus, clear-cut LI to a 25 gram dose of lactose was observed in these nine children. On a lactose dosage per kg body weight basis, the 25 gram dose to 10 year olds was roughly equivalent to a 50 gram dose for middle age adult subjects.

Summary.

What amount of daily lactose intake is tolerable in subjects with diagnosed lactose intolerance? How does this differ by age and ethnicity? What are the diagnostic standards used? A number of problems arose when we attempted to answer these seemingly straightforward questions via a review of the existing literature.

1. Patients enrolled in the studies did not have "diagnosed lactose intolerance." The standard approach to the classification of patients enrolled in studies of intolerance was the demonstration via hydrogen breath testing or blood glucose measurements that the subject incompletely absorbed a sizable dosage of lactose (30 to 50 grams). While most studies recorded symptoms with this dosage of lactose, this information was seldom used in the selection of study subjects. Thus, the vast majority of the studies investigated subjects with proven LM, not proven LI.
2. Although very seldom discussed in the literature, tests for LM are not 100 percent accurate. Most studies used H_2 breath testing to identify lactose malabsorbers. It is known that this test has an appreciable, but not well defined, false negative rate, i.e., subjects with LM do not generate a diagnostic rise in breath H_2. The incidence of false positives, i.e., production of the H_2 in the small bowel with complete absorption of lactose, is not known. Thus, some patients were incorrectly classified as lactose malabsorbers or absorbers.
3. The taste of conventional milk and lactose hydrolyzed milk differ. Many studies did not disguise this taste difference.
4. Lactose was administered in a variety of ways in the intolerance tests. Most studies fed lactose in water or milk as a single does in the fasting state upon arising in the morning. The daily tolerable dose of lactose appears to be greater if lactose intake is distributed throughout the day and taken with meals.
5. The response to lactose is primarily subjective symptoms – i.e., abdominal discomfort, gas, bloating – the severity of which the subjects rated on numerical scales. The finding of a statistically significant increase in symptoms with the lactose containing product versus the low lactase product was considered to provide evidence of intolerance. However, the biological significance of changes in numerical rating seldom was investigated. Only one study attempted to evaluate the association between the symptom score and the global assessment of symptom severity. In this study, the majority of a group of subjects who had a significant increase in symptom score when high and low lactose test periods were compared did not clearly identify the high lactose period as being particularly symptomatic.
6. Some data supports the belief that the routine ingestion of lactose increases the quantity of lactose that is tolerable. Very few studies provided data on lactose ingestion by subjects prior to enrollment in controlled trials.

With the above problems in mind, the literature on this question can be summarized as follows: As shown in Figure 12, the majority of studies indicate that subjects with “lactose intolerance” can ingest 12 grams of lactose as a single dose (particularly if taken with food) with no or minor symptoms. In contrast, when lactose/milk is administered as a single test dose without other nutrients, dosages of 12 grams may be symptomatic (Figure 13). As the dose is increased above 12 grams, intolerance becomes more prominent, with single doses of 24 grams usually yielding appreciable symptoms. There is some evidence that if 24 grams of lactose are distributed throughout the day, many lactose malabsorbers will tolerate this dosage. Lactose in a dose of 50 grams induces symptoms in the vast majority of subjects. While the literature is laden with studies of the relationship of ethnicity to lactose malabsorption, no studies made it possible to determine if lactose malabsorbers of differing ethnicities have differing tolerance to lactose. Likewise, there was no data on the relationship of age or sex to the quantity of lactose that can be tolerated by lactose intolerant subjects.

Figure 12. **Symptomatic response[#] of adult lactose malabsorbers to lactose ingested with nutrients other than milk**

Publication	0	3	6	7	9	12	15	18	22	30	34	42	49	50	55	63	70
Cheng, 1979[128] (n=15)*														++			
Suarez, 1998[110] (n=31)											+						
Vesa, 1997[132] (n=30)								-									
Jones, 1976[130] (n=16)				-			-			++							
Rorick, 1979[116] (n=23)						-											
Suarez, 1997[111] (n=19)									-								
Suarez, 1995[113] (n=21)						-											
Newcomer, 1978[120] (n=59)	-	-	-		-	-		-						++			
Hertzler, 1996[118] (n=18)												-	-		-	-	-

[#] Symptoms indicated by: - no or trivial symptoms; + minor symptoms; ++ severe symptoms
* n indicates number of lactose malabsorbing subjects studied

Figure 13. Symptomatic response[#] of adult lactose malabsorbers to lactose ingested without nutrients other than milk

Publication	0	2	3	6	8	10	12	13	14	15	16	17	19	20	23	24	25	29	30	49	50	100
Rosado, 1984[133] (n=25)*													+									
Kwon, 1980[127] (n=45)									-									+				
Cavalli-Sforza, 1987[122] (n=40)					±			±								+						
Reasoner, 1981[125] (n=9)																			+	++		
Rask Pedersen, 1982[124] (n=17)															+							
Lybeck Sorensen, 1983[134] (n=35)		-	-				-								-	+					++	
Johnson, 1993[114] (n=45)												+										
Jones, 1976[130] (n=17)						-											+				++	
Xenos, 1998[121] (n=8)																						++
Montalto, 2005[108] (n=20)														++								
Hertzler, 1996[118] (n=13)	-	-		-										++								
Stephenson, 1974[131] (n-19)										-									+		++	
Brand, 1991[115] (n=26)											+											

[#] Symptoms indicated by: - no or trivial symptoms; + minor symptoms; ++ severe symptoms
* n indicates number of lactose malabsorbing subjects studied

Key Question 4. What strategies are effective in managing individuals with diagnosed lactose intolerance?

The details of our search strategy are presented in the methods section and in Figure 2. A total of 37 unique randomized studies (26 on lactase/lactose hydrolyzed milk supplements, lactose reduced milk, eight on probiotics, two on incremental lactose dose for colonic adaptation, and one on other agents) met inclusion criteria.[108-147] The quality of the studies was low, with almost no study reporting adequate allocation concealment. Generally, studies had small sample sizes and reporting of symptoms was variable or not reported: composite scores of four to five symptoms or individual symptoms such as abdominal pain, diarrhea, bloating, and flatulence were reported, either as means or proportion. Many studies enrolled individuals who did not have a prior diagnosis of LI or did not have a prior history of LI like symptoms.

We focused our results on strategies grouped in the following categories, discussed below:

- Commercially available lactase/lactose hydrolyzed milk or nonlactose solutions and other dietary strategies
- Prebiotics and probiotics
- Incremental lactose for colonic adaptation
- Other strategies

Commercially Available Lactase/Lactose Hydrolyzed Milk, or Nonlactose Solutions

Characteristics of included studies. There was one study representing two trials that tested lactase supplements Lactodigest, DairyEase, and Lactaid,[136] while the remaining 25 studies reported on lactose reduced or hydrolyzed milk by adding a lactase enzyme such as beta-galactosidase to the milk. Studies enrolled between six and 150 subjects. Women constituted 56 percent of the subjects (n=23 studies). The mean age of subjects was 37 years of age, with a range between 10 and 77 (n=19 studies). Six trials included children or adolescents.[109,114,123,126,127,135] One trial enrolled elderly subjects (mean age 77 years).[116] Within the 19 studies reporting race or ethnicity, 40 percent of subjects were white, 30 percent Hispanic, 20 percent black, and 9 percent Asian.[109-116,123,126-130,133-135,137] Nineteen studies utilized commercial lactase products or hydrolyzed milk,[108-111,113-115,121-125,128,133,135,136] two used milk products with lactose removed by ultrafiltration or chromatographically,[112,134] and five assessed nonlactose solutions.[116,126,127,137,138] Unclear or unreported methods of lactose removal were noted in two trials[129,132] Subjects in 18 studies reported abdominal symptoms compatible with malabsorption of lactose prior to study entry.[108-114,121,123-125,128,130,132,134,136-138] Abdominal symptoms were not required for study participation (based solely on biochemical diagnosis) or subjects were not reported to experience symptoms following ingestion of lactose in ten studies.[115,116,122,126,127,129,130,133,135,136] LM was diagnosed following lactose tolerance tests by the hydrogen breath test in 11 of the studies[108-116,136] and blood glucose test in 13 studies[121-130,137,138] Diagnosis based on urinary galactose concentration was reported in one study[132] and biochemical method of diagnosis was not reported in three trials.[133-135] Over half of the trials included lactose digesting controls.[110-113,116,122,125-129,133,135,137]

Among the 18 studies that enrolled symptomatic subjects at baseline, 13 utilized lactose doses greater than 12 grams, comparable to one cup of milk.[108,110,111,114,121,123-125,128,130,132,134,136,137]

Hydrolyzed lactose doses typically ranged from zero to two grams per dose. In most of the studies, the lactose dose was consumed in a single serving. In six trials, the lactose dose was administered over multiple intervals per day for at least part of the study.[110,111,122,125,128,132]

Results. We found insufficient evidence that lactose reduced solution/milk, with lactose content of 0-2 grams, is effective in reducing symptoms among individuals with LI. Seven studies, representing nine comparisons that enrolled individuals who had symptoms compatible with LI reported inconsistent results that lactose reduced preparations reduced overall symptom scores compared to controls. None of the four studies reported a significant improvement in overall symptoms compared to control preparations of up to 12 grams of lactose. However, as noted in key question 3, doses of 12 grams of lactose or less are well tolerated and produce minimal to no symptoms. When compared to controls given greater than 12 grams of lactose, only two out of five trials reported statistically significant reductions in overall symptoms with lactose reduced/ hydrolyzed milk. Results for individual symptoms of abdominal pain, diarrhea, flatulence, and bloating were also inconsistent.

For all included studies, regardless of symptom history, information from 16 (19 comparisons), mostly low quality, trials was insufficient to determine the effect of hydrolyzed milk, lactase, or non lactose preparations in reducing GI symptoms compared to lactose controls. Some studies did report substantial reductions (improvement from moderate and severe to mild or none, or an absolute reduction of at least 50 percent) in abdominal pain/cramping[109,112,123,125,134] and diarrhea[136] with use of lactose reduced solution/milk, with lactose content of 0-2 grams, compared to a lactose dose of 12 grams or more. However, even in studies where symptoms were reduced, statistically significant reductions were not consistently observed among all symptoms reported, or only a subset of symptoms was reported. For example, the overall symptom score was significantly reduced by 60 percent with 591 milliliters of lactose reduced milk containing 7.5 grams of lactose compared to a similar amount of milk with 30 grams of lactose,[130] and by 13 percent with low lactose skim milk with 0.8-6.5 grams of lactose compared to skim milk with 6.1-49 grams of lactose,[122] but the subjects in both studies were not symptomatic at enrollment, and improvement in individual symptoms was not provided. Mean and total symptom scores were also reduced, from 3.7 to 0.36 with 70 percent hydrolyzed milk compared to placebo with 20 grams of lactose,[108] but subjects were also not symptomatic at enrollment, and improvement in individual symptoms was not provided. One study reported a score of 46 for skim milk with 11.3 grams of lactose which was reduced to a score of 17 with low lactose milk with 3.2 grams of lactose, but the difference was not statistically significant.[134] Similar reductions were seen in summed scores for abdominal pain from 43 with milk containing 25 grams of lactose to one with lactose hydrolyzed milk containing 1.25 grams of lactose[123] and a mean score for abdominal pain from 7.5 with milk containing 12 grams of lactose to 4.1 with milk containing lactase,[109] both in children. Again, neither study required subjects to be symptomatic at baseline. One study showed a statistically significant reduction in abdominal pain from moderate to none or mild with low lactose milk containing 2.9 grams of lactose compared to skim milk containing 28.5 grams of lactose.[125] One trial found a significantly greater percentage of subjects reporting abdominal pain and bloating compared to the 0.5 grams and 1.5 grams doses, respectively.[112] Compared to placebo, use of lactase supplement Lactodigest, DairyEase, or Lactaid in doses of two to four capsules/tablets when taken with 400 ml of 2 percent milk containing 20 grams of lactose reduced overall symptom scores in subjects not symptomatic at enrollment. Of greater clinical relevance to management of patients with symptoms compatible with LI who wish to consume doses of lactose beyond the minimally tolerable dose, these products were found not to reduce symptoms when administered with a dose of 50 grams of lactose in

subjects who had symptoms compatible with LI.[136] Generally, studies had small sample sizes and reporting of symptoms was variable: composite scores of four to five symptoms or individual symptoms such as abdominal pain, diarrhea, bloating, and flatulence were reported, either as means or proportion, making pooling estimates difficult.

Prebiotics and Probiotics

Characteristics of included studies. Eight randomized trials were included; (Appendix Table D9) seven crossover[117,139-141,143-145] and one parallel group design.[142] The trials were generally small, enrolling between nine and 28 subjects (Table 18). Among the five studies reporting gender, women constituted 34 percent of the subjects.[139-143] Two studies enrolled only male subjects.[142,143] Subjects were typically young to middle-aged adults (between 18 and 45 years old), and only one study enrolled subjects older than 60 years of age.[144] Half of the studies reported race or ethnicity. White subjects comprised two trials,[140,141] one study evaluated black African immigrants to France,[142] and one trial was conducted in Taiwan Chinese.[117] Five of the studies were conducted in the United States,[139,140,143-145] two in France,[141,142] and one in Taiwan.[117] Five trials assessed probiotic test products, prepared by adding strains of lactobacillus acidophilus, lactobacillus bulgaricus, or bifidobacterium longum to milk prior to consumption.[117,139,140,144,145] Four studies evaluated yogurt products.[141-143,145] LM was diagnosed by the hydrogen breath test in all studies.

Results. We found insufficient evidence to determine the effectiveness of yogurt or probiotics to improve lactose intolerance symptoms (Table 19). The inclusion criteria and the studied type of yogurt and probiotics were variable—results either did not show a difference in symptom score, or reported clinically insignificant differences, mostly in the symptoms that are of low clinical relevance, such as flatulence. Only one study noted that the enrolled subjects reported symptoms compatible with malabsorption of lactose prior to study entry[144] and reported no difference in symptom score in groups given milk or acidophilus milk (symptom score of 40 in both groups). In the remaining studies, study entry was based solely on breath hydrogen tests, and subjects were not reported to experience symptoms following ingestion of lactose. Lactose doses in the control tests were between 10 and 20 grams. Overall symptom score was reduced from 12.5 with 2 percent milk containing 20 grams of lactose to 2.8 with the same milk formulation but with added lactobacillus at 10^9 cfu/ml.[117] Similar improvements were seen with the addition of lactobacillus at 10^8 cfu/ml (overall score 3.9) and lactoacidolphilus at 10^9 cfu/ml (overall score 6.5), but not with lactoacidolphilus at 10^8 cfu/ml. Overall symptom scores improved from fairly strong to mild with 400 ml of bulgofilus milk (Ofilus bacteria+L. bulgaircus) compared to control (lactulose 10 grams in 250 ml water), both with 18 grams of lactose.[141] Reductions in other symptoms such as abdominal pain and diarrhea were either not reported, not significantly different, or of low clinical significance or relevance. The inclusion criteria were variable, the type, source, and concentration of yogurt and probiotics studied were variable, and no two studies studied the same agent. Based on these findings we found insufficient evidence for the use of yogurt or probiotics for lactose intolerance.

Incremental Lactose for Colonic Adaptation

We found insufficient evidence to support the role of incremental doses of lactose for lactose intolerance symptoms (Table 19). Two studies met our inclusion criteria.[118,146] In the first one, 20 healthy volunteers with LM on hydrogen breath testing were randomized to receive either dextrose

or lactose in a blinded fashion for 10 days and crossed over for days 12 through 21. The dose of lactose and dextrose was 0.6 grams/kg body weight per day, increased by 0.2 grams/kg/day to a maximum of 1 gram/kg/day (approximately 42 to 70 grams of lactose per day for an average 70 kg adult). Subjects were also given lactose challenge doses of 0.35 grams/kg on days 11 and 22. The authors found that symptoms of flatulence after the lactose challenge decreased by 50 percent after lactose feeding compared to dextrose feeding, while symptoms of abdominal pain and diarrhea did not differ. These results suggest that colonic adaptation may occur, but there is no appreciable decrease in clinically relevant symptoms of abdominal pain and diarrhea. Though subjects were lactose malabsorbers at baseline, average symptom scores were 1 (scale 0-5) even with the highest doses of lactose (70 grams), and very similar to scores were seen with sucrose. The second study evaluated colonic adaptation to lactose compared to sucrose in a double blinded fashion. The study enrolled 46 healthy volunteers in France, 21 males, 25 females, all of Asian origin, with a mean age of 33 (range 20-47 years) that were lactose malabsorbing by hydrogen breath testing. Subjects were fed their regular diet and underwent hydrogen breath testing and symptom evaluation on days 1 and 14. For the 13 days in between, subjects were fed either 34grams of lactose or sucrose in a double blind fashion. The overall clinical score improved from 42 to 20 in the group randomized to lactose, as did the individual mean scores for pain, flatulence, bloating and borborygmi, but similar improvements were seen with sucrose (overall score improvement from 42 to 24), suggesting a placebo response.

Other Strategies

We found insufficient evidence regarding rifaximin for treatment of lactose intolerance. A single small study met inclusion criteria[147] and showed reduction in symptom score after rifaximin treatment compared to placebo and similar to a lactose free control. The study enrolled 40 patients with lactose malabsorption on hydrogen breath test, 16 were randomized to 10-day treatment with rifaximin 800 mg/day, 16 to a 40-day lactose free diet, while eight were given 10 days of placebo. On a scale of 0-4, compared to baseline, there was reduced abdominal pain (2.0 versus 1.0), diarrhea (1.3 versus 0.2), bloating (2.5 versus 1.6), and distention (2.4 versus 1.5) at day 40 for the rifaximin group. Similar decreases were seen for the lactose free group. The clinical significance of the change in score is not clear.

Studies on Management Strategies in Subjects with IBS and LM/LI

We found insufficient evidence that low lactose diet or probiotics were effective in reducing symptoms of lactose intolerance among subjects with IBS and LM/LI. Four small, double blinded, trials assessed management strategies in subjects with IBS and LI/LM with conflicting results.[144,175-177] A British study of 23 IBS subjects identified with lactose malabsorption based on the hydrogen breath test found patients with LI were not distinguishable from other IBS subjects based on GI symptoms, and treatment with a low lactose diet led to disappointing results.[175] They concluded there was no real advantage to segregating IBS subjects with LI from other IBS subjects. In contrast, a Dutch study investigating the prevalence of lactose malabsorption in 70 IBS patients found statistically significant improvement in GI symptoms in 17 IBS subjects identified to have LM following 6 weeks of treatment with a low lactose diet.[176] They concluded that LM should be excluded prior to a diagnosis of IBS. A Mexican study of 12 IBS subjects, eight of whom were noted to be lactase nonpersistent, found that IBS symptoms appeared to be

independent of LM following 3 months of treatment with hydrolyzed milk or placebo.[177] An American study by Newcomer assessed whether unfermented acidophilus milk was beneficial in relieving symptoms in subjects with lactase deficiency or IBS.[144] Sixty one subjects with IBS who were lactase sufficient and 18 lactase deficient (based on the hydrogen breath test) subjects each received lactobacillus acidophilus milk or regular milk for 2 week intervals each. Within the lactase deficient group, symptoms were not significantly reduced during the acidophilus milk period compared to the regular milk period. In subjects with IBS, acidophilus milk did not relieve their symptoms. These studies are summarized in Table 19, section F.

Figure 14. Percentage of subjects reporting abdominal pain

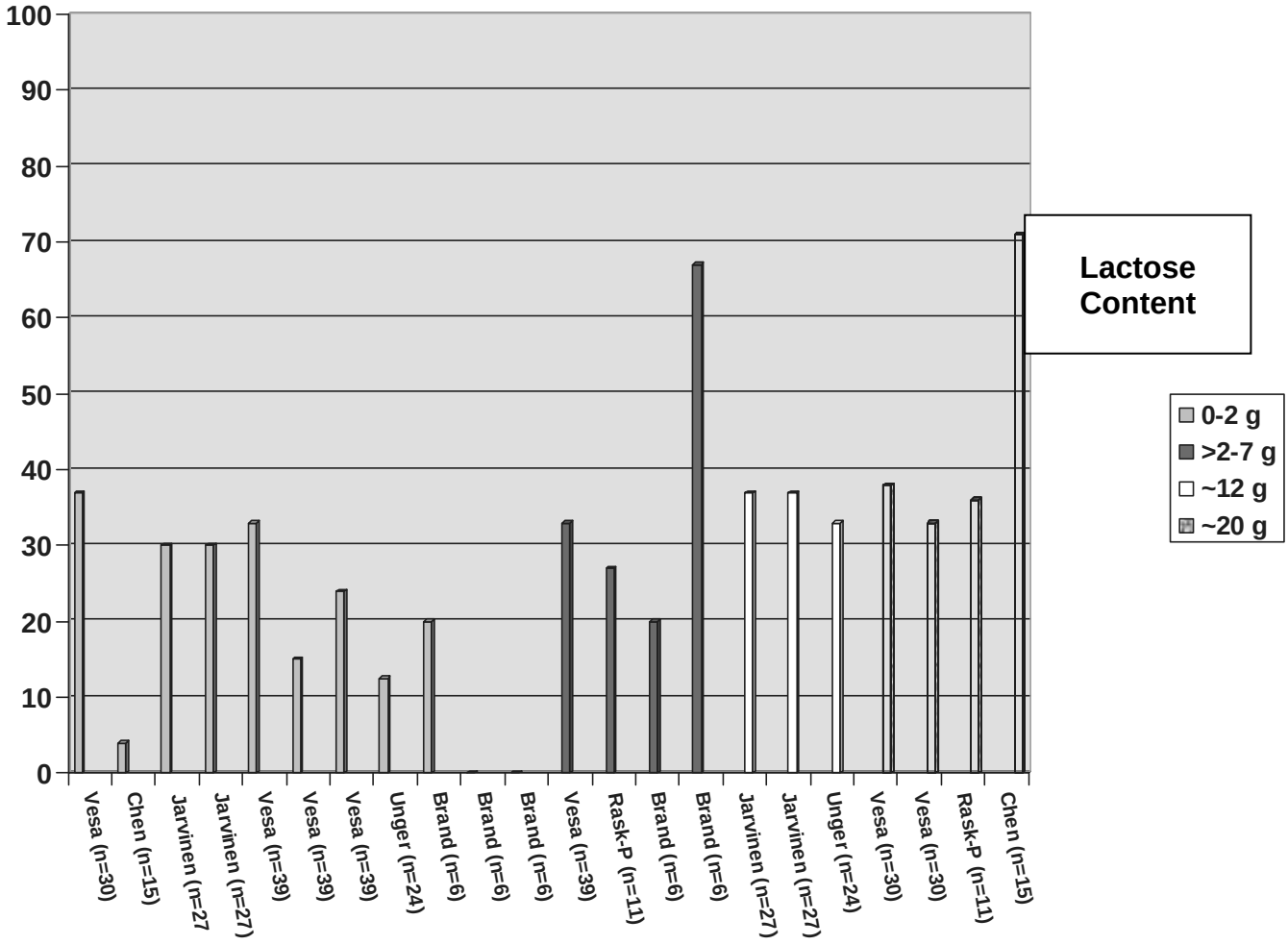


Figure 15. Abdominal pain based on symptom scores (0 = none, 1 = mild, 3 = moderate, 5 = severe)

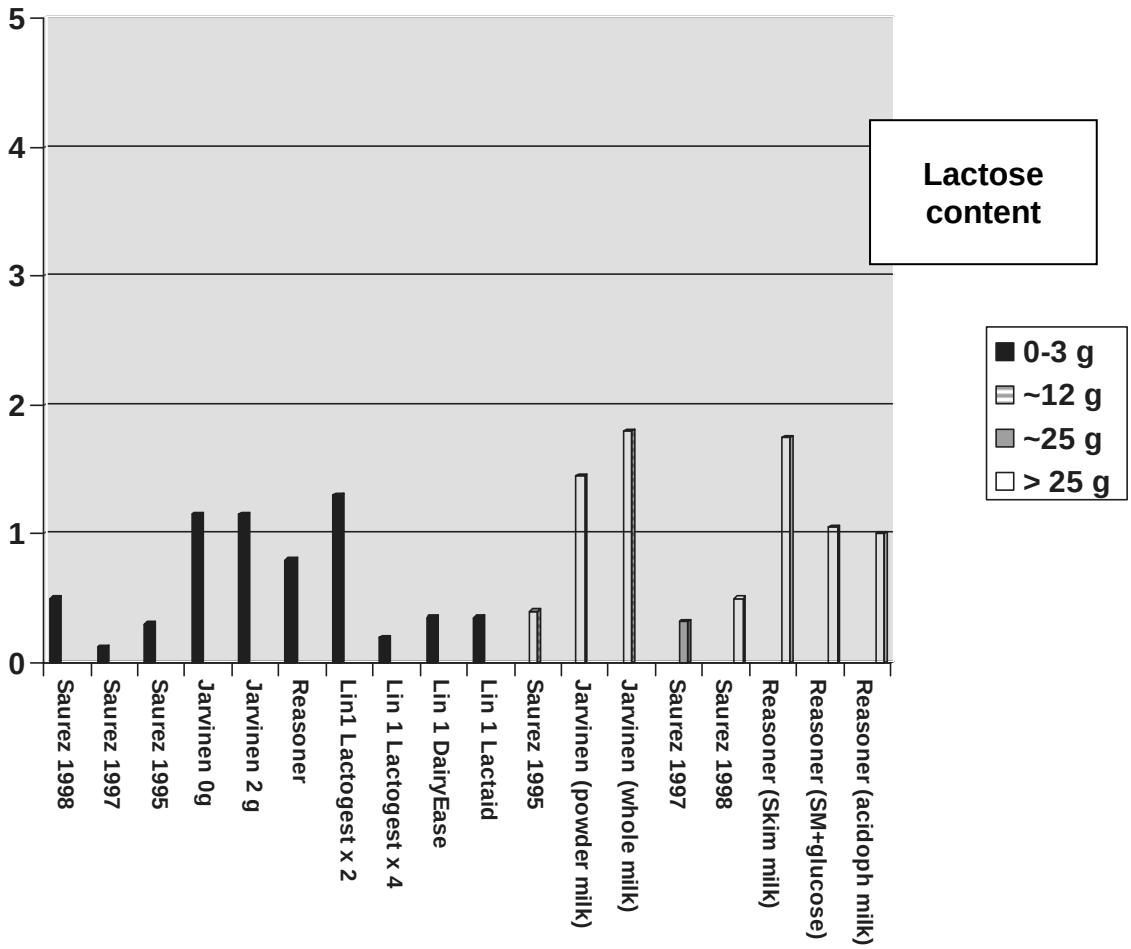


Table 18. Summary of study characteristics for blinded LI treatment studies

Characteristic	Range (Number of Subjects, Percent, or Mean)	Number of Studies Reporting
A. Commercially-available lactase/lactose hydrolyzed milk, or nonlactose solutions		
Total number of studies	6 to 150	28 (26 publications)
Studies with lactose tolerant controls (number of controls)	5 to 64	14
Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion or unclear	6 to 150	10
Studies with children (range)	9 to 150	6 (4 exclusive)
Mean age (range)	37 (10 to 77)	19
Gender, female – mean % (range)	56 (0 to 93)	23
Race/ethnicity, White - mean % (range)	40 (0 to 100)	19 (1 exclusive)
Race/ethnicity, Hispanic* - mean % (range)	30 (0 to 100)	19 (3 exclusive)
Race/ethnicity, Black - mean % (range)	20 (0 to 100)	19 (2 exclusive)
Race/ethnicity, Asian - mean % (range)	9 (0 to 100)	19 (1 exclusive)
Studies conducted in the United States	11 to 110	15
Diagnosis, hydrogen breath test	11 studies	
Diagnosis, blood sugar test	13 studies	
Diagnosis, urinary galactose test	1 study	
Noted as “double-blind” studies (some studies noted that it may not be possible mask flavors of tests)	24 studies	
Single blind studies	4 studies	
Multi-dose studies (test products administered more than one time/day)	6 studies	
B. Prebiotic/probiotic studies		
Total number of studies	9 to 28	8
Studies with lactose tolerant controls (number of controls)	10	1
Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion	9 to 28	7
Age range of subjects	18 to 69	7
Gender, female - mean % (range)	34 (0 to 73) (2 exclusively male)	5
Race/ethnicity, White - mean % (range)	45 (0 to 100)	4 (2 exclusive)
Race/ethnicity, black - mean % (range)	24 (0 to 100)	4 (1 exclusive)
Race/ethnicity, Asian - mean % (range)	30 (0 to 100)	4 (1 exclusive)
Number of studies conducted in the United States	9 to 28	5
Diagnosis, hydrogen breath test	All studies	
Noted as “double blind” studies (some studies noted that it may not be possible to mask flavors of tests)	5 studies	
Single blind or blinding unclear studies	3 studies	
D and E. Colonic adaptation and incremental lactose load studies/studies with different levels of lactose		
Total number of studies	13 to 59	4
Studies with lactose tolerant controls (number of controls)	19	1
Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion	All studies	
Age range of subjects	23 (19 to 32)	3
Gender, female - mean % (range)	46 (25 to 54)	4
Race/ethnicity, Non-white - mean % (range)	51 (29 to 90) Asian 70% in one trial	2
Race/ethnicity, White - mean % (range)	49 (10 to 71)	2
American Indian	59 (1 exclusive)	
Number of studies conducted in the United States	All studies	
Diagnosis, hydrogen breath test	3 studies	
Diagnosis, blood sugar test	1 study	
Noted as “double blind” studies (some studies noted that it may not be possible to mask flavors of tests)	2 studies	
Single blind or blinding unclear studies	2 studies	

*Subjects could be of any race

Table 19. Occurrence of GI symptoms in randomized trials

I. Studies that reported subjects with symptoms at baseline in addition to LI by biochemical testing

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
A. Commercially-available lactase/lactose hydrolyzed milk, or nonlactose solutions								
A1. Studies with doses of lactose >12 g per dose/test								
Montalto, 2005[108] *(n=30)*		**Mean clinical score (± SD) based on symptoms: 0=absent to 3=severe for bloating, abdominal pain, flatulence, diarrhea for each during test**						
Test A –enzyme (3,000 UI), added 10 hours prior to consumption	≥70% hydrolyzed	0.36 ± 0.55 p<0.001 vs. pbo p=0.03 vs. TB	Not Reported (NR)	NR	NR	NR	NR	NR
Test B-enzyme (6,000 UI) (TB), add 5 minutes prior	≥70% hydrolyzed	0.96 ± 0.85 p<0.001 vs. pbo	NR	NR	NR	NR	NR	NR
Placebo (pbo)	20 g	3.77 ± 0.79	NR	NR	NR	NR	NR	NR
Saurez, 1998[110] *Maldigesters (n=31)*		**Average daily severity of symptoms, (Mean ± SEM), ranked on a continuous scale from 0=no symptoms to 5=severe symptoms. Frequency "*f*" (episodes per day) reported for flatus and diarrhea)**						
Baseline		NR	NR	0.2 ± 0.1	0.4 ± 0.1	0.5 ± 0.1 10.6 ± 2.0 *f*	NR	0.02 ± 0.02 *f*
Lactose hydrolyzed products (LH)	2 g	NR	NR	0.5 ± 0.2	1.0 ± 0.3	0.8 ± 0.2 10.7 ± 1.3 *f*	NR	0.11 ± 0.08 *f*
Conventional dairy products	34 g	NR	NR	0.5 ± 0.2	1.1 ± 0.2	1.3 ± 0.2 p<0.05 vs. LH 17.1 ± 2.1 *f* p<0.05 vs. LH	NR	0.17 ± 0.09 *f*
Digesters (n=31)								
Baseline		NR	NR	0.1 ± 0.03	0.3 ± 0.1	0.4 ± 0.1 13.7 ± 1.9 *f*	NR	0.07 ± 0.05
Lactose hydrolyzed products	2 g	NR	NR	0.1 ± 0.05	0.3 ± 0.1	0.4 ± 0.1 12.8 ± 1.5 *f*	NR	0.07 ± 0.04
Conventional dairy products	34 g	NR	NR	0.1 ± 0.04	0.3 ± 0.1	0.4 ± 0.1 14.7 ± 1.9 *f*	NR	0.07 ± 0.01
Xenos, 1998[121] *(n=8)*		**Subjects reporting symptoms based on ratings (0=none to 4=severe) after consumption of each lactose dose over 24 hours**						
β-D-galactosidase 100 u/ml + 100 g lactose dissolved in water	-	NR	NR	1: 1 subject 2: 1	1: 3 2: 2	1: 2 2: 1 3: 1	2: 1 3: 2 4: 1	0: 8
Placebo + 100 g lactose dissolved in water	100 g	NR	NR	1: 1 2: 1 3: 1 4: 3	1: 1 2: 2 3: 1 4: 1	2: 2 3: 4 4: 2	1: 1 2: 2 3: 3 4: 2	1: 1 2: 1 3: 4 4: 2

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Saurez, 1997[111] *Lactase-nonpersistent, described as severely LI (n=19)*		**Mean symptom severity scores (± SEM) ranked scale on a scale as follows: 0=none; 1=trivial; 2=mild; 3=moderate; 4=strong; 5= severe. *Data were extracted from graph.* Frequency "*f*" (episodes per day) reported for flatus and diarrhea)**						
Lactose hydrolyzed milk	0 g	NR	NR	~ 0.12 ± 0.05	~ 0.14 ± 0.05	~ 0.78 ± 0.1 ~9.8 ± 1.4 *f*	~ 0.27 ± 0.09	~ 0.1 ± 0.09 *f*
Milk	23.6 g	NR	NR	~ 0.32 ± 0.1	~ 0.27 ± 0.09	~ 1 ± 0.1 ~14.4 ± 2 *f*	~ 0.6 ± 0.1	~ 0.2 ± 0.09 *f*
Lactase-nonpersistent who denied LI (n=13)								
Lactose hydrolyzed milk	0 g	NR	NR	~ 0.05 ± 0.01	~ 0.05 ± 0.002	~ 0.3 ± 0.09 ~5.7 ± 1.9 *f*	~ 0.07 ± 0.02	~ 0.05 *f*
Milk	23.6 g	NR	NR	~ 0.09 ± 0.09	~ 0.23 ± 0.1	~ 0.57 ± 0.09 ~8 ± 1.3 *f*	~ 0.18 ± 0.07	~ 0.05 *f*
Vesa, 1997[132] *(n=30)*		**Percentage of subjects who experienced symptoms after consumption of each lactose dose over 2 days**						
Lactose-free, fat-free milk	0 g	NR	NR	37	40	63	NR	NR
Fat-free milk	19.6 g x 2 days	NR	NR	38	45 p<0.05 vs. MFP	79 p<0.01 vs. MFP	NR	NR
High-fat milk	19.6 g x 2 days	NR	NR	33	33	70 p<0.05 vs. MFP	NR	NR
Milk-free period (MFP)	-	NR	NR	27	19	41	NR	NR
Johnson, 1993[114] *(n=45)*		**Presence of symptoms (abdominal fullness, cramps, flatulence, borborygmi, nausea, vomiting, diarrhea) consistent with LM**						
Lactose hydrolyzed milk	0 g	NR	15 (33%)	NR	NR	NR	NR	NR
Milk	16.4 g	NR	30 (67%) only milk 15 (33%) both	NR	NR	NR	NR	NR
Lin, Study 2, 1993[136] *(n=11)*		**Symptom scores are expressed as the sum of mean scores rating symptoms from 1 (none) to 5 (worst ever experienced) at baseline and 4 and 8 hours after challenge**						
L 50 g in water plus Lactodigest (2 capsules)	-	NR	NR	2.5	4.4	5.4	3.5 *cramps*	3.4
L 50 g in water plus DairyEase (2 capsules)	-	NR	NR	3.4	4.6	5.6	3.0 *cramps*	2.6
L 50 g in water plus Lactaid (2 capsules)	-	NR	NR	3.1	5.2	6.1	3.3 *cramps*	3.2
L 50 g in water plus Lactodigest (4 capsules)	-	NR	NR	3.2	4.0	4.7	3.3 *cramps*	2.5

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lactose (L) 50 g in water plus placebo	50 g	NR	NR	3.0	4.1	4.8	2.7 *cramps*	2.9
Nielsen, 1984[123] *(n=9 children)*		**Summation of observed symptoms from the scoring charts. At 10 times during the 24 test periods, a 0 was recorded in the scoring chart to indicate no symptoms and a 1 was recorded if symptoms were observed.**						
Lactose hydrolyzed milk (LHM)	1.25 g	NR	NR	1	NR	15	2	NR
Milk	25 g	NR	NR	43 p<0.01 vs. LHM	NR	37	37 p<0.01 vs. LHM	NR
Cheng, 1979[128] *Intolerants n=15*		**The incidence and severity of symptoms**						
Lactose hydrolyzed skim milk	0.5-1.25 g	NR	NR	279 none 9 mild 2 severe	251 none 32 mild 7 severe	252 none 25 mild 13 severe	NR	283 none 2 mild 5 severe
Skim milk	25 g	NR	NR	12 none 12 mild 18 severe	2 none 2 mild 38 severe	3 none 4 mild 35 severe	NR	6 none 13 mild 23 severe
Tolerants n=16								
Lactose hydrolyzed skim milk	0.5-1.25 g	NR	NR	324 none 4 mild 4 severe	304 none 20 mild 8 severe	311 none 12 mild 9 severe	NR	329 none 2 mild 1 severe
Skim milk	25 g	NR	NR	46 none 1 mild 1 severe	40 none 7 mild 1 severe	42 none 5 mild 1 severe	NR	47 none 1 mild 0 severe
A2. Studies with doses of lactose ≤12 g per dose/test								
Gremse, 2003[109] *(n=30 children)*		**Severity of each symptom was graded from 0=none to 4=severe. Sum of the individual symptom scores (±xx) was calculated for each 14-day study and averaged for all patients**						
Milk + lactase	-	NR	NR	4.1 ± 1.4 p=0.021 vs. M	0.9 ± 0.4	3.3 ± 2.6	NR	2.4 ± 1.1
Milk (M)	12 g	NR	NR	7.5 ± 2.7	1.4 ± 0.7	5.1 ± 2.8	NR	2.5 ± 1.1
Järvinen, 2003[138] *(n=27)*		**Subjects reporting symptoms during 8 hours after consuming chocolate samples**						
Chocolate sample consisting of lactose-free milk powder.	0 g	NR	19 (70%)	8 (30%)	16 (59%)	19 (70%)	9 (33%)	NR
Chocolate sample consisting of low-lactose milk powder	2 g	NR	22 (81%)	8 (30%)	17 (63%)	18 (67%)	10 (37%)	NR
Chocolate sample consisting of whole milk powder	12 g	NR	23 (85%)	10 (37%)	19 (70%)	21 (78%)	9 (33%)	NR
Chocolate sample consisting of fresh whole milk	12 g	NR	25 (93%) p=0.21 across groups	10 (37%) p=0.88	19 (70%) p=0.80	22 (81%) p=0.48	11 (41%) p=0.93	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
		Mean (± SD) of the scores given for symptoms. Symptoms were recorded on a questionnaire with a scale ranging from 0 (none) to 10 (very severe, disturbing normal life) once every hour for the first 3 hours and then two more times (at 4 – 6 and 7 – 8 hours) until 8 hours had elapsed.						
Chocolate sample consisting of lactose-free milk powder	0 g	13.5 (15.8) *Sum of all symptoms*	NA	2.3 ± 5.2	4.6 ± 5.5	4.4 ± 4.6	1.3 ± 2.3	NR
Chocolate sample consisting of low-lactose milk powder	2 g	16.6 ± 15.8	NA	2.3 ± 4.5	5.6 ± 6.3	5.1 ± 5.8	1.9 ± 3.2	NR
Chocolate sample consisting of whole milk powder	12 g	17.5 ± 18.6	NA	2.9 ± 5.5	5.3 ± 5.7	5.2 ± 5.4	2.1 ± 3.8	NR
Chocolate sample consisting of fresh whole milk	12 g	19.5 ± 20.8 p=0.59 across groups	NA	3.6 ± 6.6 p=0.85	5.0 ± 5.7 p=0.93	6.0 ± 6.4 p=0.75	3.4 ± 5.8 p=0.43	NR
Vesa, 1996[112] *Maldigesters (n=39) Note: not all subjects reported at the 3 hour period)*		**Percentage of subjects who experienced symptoms after each lactose dose, either 3 hours or 1 day after consumption of test. Symptom score represents the sum of symptoms, based on 0=none to 40=all, very severe (*data were extracted from graph*).**						
Percentage of subjects who reported daily or almost daily symptoms before the study		NR	NR	14	16	47	8	17
Lactose-free milk	0 g	7.7 ± 2.3	NR	15 (3 h) 33 (1 d)	22 (3 h) 44 (1 d)	19 (3 h) 51 (1 d)	10 (3 h) 18 (1 d)	NR
Lactose free milk plus 0.5 g lactose	0.5 g	5.1 ± 3.7	NR	12 (3 h) 15 (1 d) p<0.05 vs. 0 g	7 (3 h) p<0.05 vs. 0 g 28 (1 d)	19 (3 h) 49 (1 d)	16 (3 h) 28 (1 d)	NR
Lactose free milk plus 1.5 g lactose	1.5 g	4.1 ± 4.9	NR	18 (3 h) 24 (1 d)	19 (3 h) 26 (1 d) p<0.05 vs. 0 g	23 (3 h) 47 (1 d)	13 (3 h) 13 (1 d)	NR
Lactose free milk plus 7 g lactose	7 g	6.2 ± 4.6	NR	21 (3 h) 33 (1 d)	26 (3 h) 38 (1 d)	35 (3 h) 51 (1 d)	13 (3 h) 23 (1 d)	NR
Digesters (n=15)								
Percentage of subjects who reported daily or almost daily symptoms before the study			NR	0	7	27	7	0
Lactose free milk	0 g	2 ± 1	NR	8 (3 h) 13 (1 d)	0 both time points	0 (3 h) 40 (1 d)	8 (3 h) 13 (1 d)	NR
Lactose free milk plus 0.5 g lactose	0.5 g	2.7 ± 1.2	NR	8 (3 h) 13 (1 d)	0 both time points	10 (3 h) 47 (1 d)	8 (3 h) 20 (1 d)	NR
Lactose free milk plus 1.5 g lactose	1.5 g	3.8 ± 1.3	NR	0 (3 h) 7 (1 d)	0 both time points	0 (3 h) 53 (1 d)	8 (3 h) 20 (1 d)	NR

NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lactose-free milk plus 7 g lactose	7 g	1.1 ± 2	NR	0 (3 h) 7 (1 d)	0 (3 h) 7 (1 d)	0 (3 h) 40 (1 d)	0 (3 h) 7 (1 d)	NR
Saurez, 1995[113] *Malabsorbers (n=21)*		**Severity of daily gastrointestinal symptoms over the one week period (mean ± SEM), based on 0=none to 5=severe. Frequency (episodes per day reported for flatus and diarrhea)**						
Lactose hydrolyzed low fat milk	<0.5 g	NR	NR	0.3 ± 0.1	0.5 ± 0.1	0.9 ± 0.1 7.6 ± 1.2 *f*	NR	0.3 ± 0.1 *f*
Low-fat milk	12.1 g	NR	NR	0.4 ± 0.1	0.6 ± 0.1	1.1 ± 0.1 10.1 ± 1.5 *f*	NR	0.1 ± 0.0 *f*
Absorbers (n=9)								
Lactose hydrolyzed low fat milk	<0.5 g	NR	NR	0.4 ± 0.2	0.5 ± 0.2	1.2 ± 0.2 8.4 ± 1.9 *f*	NR	0.2 ± 0.1 *f*
Low fat milk	12.1 g	NR	NR	0.6 ± 0.2	0.6 ± 0.2	0.9 ± 0.2 11.8 ± 2.3 *f*	NR	0.3 ± 0.2 *f*
A3. Studies with doses of lactose >12 g and ≤12.5 g per dose/test								
Lybeck Sørensen, 1983[134] *(n=35)*		**Frequency of symptoms in percent following milk ingestion over 8 hours. Symptoms were ranked accordingly: 0=no symptoms; 1=slight; 2=moderate; 3=severe. The total symptom score was calculated as the sum of the score for each person.**						
Low lactose milk, 250 ml	1.6 g	26 Median = 0.47	*At least ≥1 moderate or severe symptom* 6		18	29	18 *cramps*	6
Low lactose milk, 500 ml	3.2 g	17 p<0.05 vs. SM 500 ml Median = 0.35	3 p<0.05 vs. SM 500 ml		14 p<0.05 vs. SM 500 ml	20 p <0.05 vs. SM 500 ml	3 *cramps* p<0.05 vs. SM 500 ml	9
Skim milk (SM), 250 ml	11.3 g	46 Median = 0.67	9		42	49	12 *cramps*	15
Skim milk, 500 ml	22.5 g	46 Median = 1.14	31		49	51	26 *cramps*	14
Rask Pedersen, 1982[124] *(n=11)*		**Subjects reporting symptoms. On a 24 hour diary sheet, subjects reported abdominal symptoms based on the following, 0=none; 1=mild/moderate; 2=severe. For diarrhea, no diarrhea=formed stools; mild/moderate= ≤3 liquid/soft stools; severe= ≥4 liquid/soft stools.**						
Low lactose milk	3.75 g	NR	NR	8 none 3 mild/mod 0 severe	NR	6 none 4 mild/mod 0 severe	*Combined with flatulence*	8 none 2 mild/mod 1 severe
Milk	25 g	NR	NR	7 none 2 mild/mod 2 severe	NR	1 none 5 mild/mod 5 severe	*Combined with flatulence*	4 none 2 mild/mod 5 severe

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Reasoner, 1981[125] *Milk intolerant group (n=9)*		**Symptom scores based on the occurrence and severity of symptoms experienced after each test meal: 0-0.33=none to mild; 0.34-0.66=moderate; 0.67-1=severe.**						
Low lactose milk	~2.9 g	NR	NR	0.16 p<0.05 vs. SM	0.23	0.40 p <0.05 vs. SM	0.11 *nausea*	NR
Skim milk (SM)	~28.5 g	NR	NR	0.35	0.26	0.57	0.04 *nausea*	NR
Skim milk plus glucose	~28.5 g	NR	NR	0.21	0.31	0.45	0.05 *nausea*	NR
Sweet acidophilus milk	~28.5 g	NR	NR	0.20	0.40	0.50	0.03 *nausea*	NR
Milk tolerant group (n=5)								
Low lactose milk	~2.9 g	NR	NR	No symptoms reported	0.06	0.32 p <0.04 vs. SM	No symptoms reported	NR
Skim milk (SM)	~28.5 g	NR	NR		0.12	0.51		NR
Skim milk plus glucose	~28.5 g	NR	NR		0.06	0.25 p <0.01 vs. SM		NR
Sweet acidophilus milk	~28.5 g	NR	NR		none	0.31 p <0.03 vs. SM		NR
Unger, 1981[178] *Malabsorbers (n=24)*		**Subjects reporting symptoms during 24 hours after consumption**						
Lactose-free chocolate dairy drink, 240 ml		NR	3 (12.5%)	NR	NR	NR	NR	NR
Lactose free chocolate dairy drink, 480 ml		NR	2 (8)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 240 ml	10.8 g	NR	8 (33)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 480 ml	21.6 g	NR	10 (42)	NR	NR	NR	NR	NR
Absorbers (n=75)								
Lactose free chocolate dairy drink, 240 ml		NR	*unclear*	NR	NR	NR	NR	NR
Lactose free chocolate dairy drink, 480 ml		NR	*unclear*	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 240 ml	10.8 g	NR	*unclear*	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 480 ml	21.6 g	NR	*unclear*	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content / Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Jones, 1976, Part II[130] *(n=17)*		**Symptoms scores and subjects reporting symptoms of bloating, gas, diarrhea and cramps using scale: 0=no symptoms, 1=mild, 2=moderate, 3=severe, summed**						
Aqueous lactose 250 ml	25 g	46	13 (76.5%)	NR	NR	NR	NR	NR
Regular skim milk 500 ml	25 g	45	15 (88.2%)	NR	NR	NR	NR	NR
Regular whole milk 500 ml	25 g	39	12 (70.6%)	NR	NR	NR	NR	NR
60% reduced skim milk 500 ml	10 g	14	6 (35.3%)	NR	NR	NR	NR	NR
60% reduced lactose whole milk 500 ml	10 g	9	7 (41.2%)	NR	NR	NR	NR	NR
Placebo 250 ml (saccharin, lemon juice water)	0 g	9	6 (35.3%)	NR	NR	NR	NR	NR

II. Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion (based on biochemical measures only)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lin, Study 1, 1993[136] (n=20)		**Symptom scores, expressed as the mean of the sum of scores rating symptoms (gas, stomach pain and/or cramps and diarrhea) from 0 (none) to 5 (severe) for each hour from baseline to 8 hr after the challenge.**						
Low fat milk plus Lactodigest (2 capsules)	20 g	4.75 p<0.05 vs. pbo	NR	1.30	NR	2.95 p<0.05 vs. pbo	NR	0.25 p <0.05 vs. pbo
Low fat milk plus DairyEase (2 capsules)	20 g	2.75 p<0.05 vs. pbo	NR	0.35	NR	2.25 p<0.05 vs. pbo	NR	0.15 p <0.05 vs. pbo
Low fat milk plus Lactaid (2 capsules)	20 g	2.60 p<0.05 vs. pbo	NR	0.35	NR	2.10 p<0.05 vs. pbo	NR	0.15 p <0.05 vs. pbo
Low fat milk plus Lactodigest (4 capsules)	20 g	1.25 p<0.05 vs. pbo, Lactodigest	NR	0.20 p< 0.05 vs. pbo	NR	1.0 p <0.05 vs. pbo	NR	0.05 p <0.05 vs. pbo
Low fat milk plus placebo (pbo)	20 g	10.45	NR	1.55	NR	7.85	NR	1.30
Brand, 1991[115] *(n=6)*		**Number of subjects who reported specific symptoms over 4 hours after consumption**						
95% lactose reduced milk	<0.25 g	NR	*At least ≥1 symptom* 0	0	NR	0	NR	0
80% lactose reduced milk (Cotee)	1 g	NR	1	1	NR	1	NR	0
80% lactose reduced milk (Balance)	1 g	NR	1	0	NR	1	NR	0

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
50% lactose reduced milk	2.4 g	NR	1	1	NR	0	NR	1
Whole milk	4.8 g	NR	5	4	NR	3	NR	3
Cavalli-Sforza, 1987[122] *Malabsorbers (n=40)*		**Percentages of the total number of tests for symptom) response (diarrhea, flatulence, bloating, or abdominal pain) during the 24 hours after consuming the milk test. Symptoms were rated none=0, mild=1, moderate=2, or severe=3 in intensity. A total for the 4 symptoms could range from 0 to 12.**						
Low lactose skim milk (all quantities) Number of tests: 159	0.8-6.5	0: 64.8%; 1: 11.3%; 2: 8.2%; 3: 4.4%; 4: 5.0%; >4: 6.3% Overall % with symptoms: 35.2% p<0.05 vs. SM for presence/ absence of symptoms; p<0.05 vs. SM for intensity of symptoms	NR	NR	NR	NR	NR	NR
Skim milk (SM) (all quantities) Number of tests: 156	6.1-49	0: 51.3%; 1: 15.4%; 2: 16%; 3: 9%; 4: 1.9%; >4: 6.4% Overall % with symptoms: 48.7%	NR	NR	NR	NR	NR	NR
Low lactose whole milk (all quantities) Number of tests: 160	0.6-5	0: 62.5%; 1: 16.9%; 2: 11.2%; 3: 3.8%; 4: 3.8%; >4: 1.8% Overall % with symptoms: 37.5% p ns vs. whole milk	NR	NR	NR	NR	NR	NR
Whole milk (all quantities) Number of tests: 151	6.4-51	0: 51%; 1: 17.2%; 2: 20.5%; 3: 4.0%; 4: 4.6%; >4: 2.7% Overall % with symptoms: 49%	NR	NR	NR	NR	NR	NR
Absorbers (n=31))								
Low- lactose skim milk (all quantities) Number of tests: 118	0.8-6.5	0: 71.2%; 1: 5.1%; 2: 5.9%; 3: 8.5%; 4: 3.4%; >4: 5.9% Overall % with symptoms: 28.8% p ns vs. SM	NR	NR	NR	NR	NR	NR
Skim milk (SM) (all quantities) Number of tests: 122	6.1-49	0: 75.4%; 1: 10.7%; 2: 5.7%; 3: 3.3%; 4: 1.6%; >4: 3.3% Overall % with symptoms: 24.6%	NR	NR	NR	NR	NR	NR
Low lactose whole milk (all quantities) Number of tests: 118	0.6-5	0: 78%; 1: 4.1%; 2: 12.6%; 3: 0.9%; 4: 1.7%; >4: 2.7% Overall % with symptoms: 22% p ns vs. whole milk	NR	NR	NR	NR	NR	NR
Whole milk (all quantities) Number of tests: 118	6.4-51	0: 77.2%; 1: 5.9%; 2: 6.8%; 3: 2.6%; 4: 1.7%; >4: 5.9% Overall % with symptoms: 22.8%	NR	NR	NR	NR	NR	NR
Malabsorbers (n=40)		**Number of subjects reporting symptoms based on the quantity of the 4 milk types**						
Low lactose skim milk 125 ml	0.81 g	NR	8/40 (20%)	NR	NR	NR	NR	NR
Low lactose skim milk 250 ml	1.6 g	NR	11/40 (27.5%)	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Low lactose skim milk 500 ml	3.25 g	NR	18/40 (45%)	NR	NR	NR	NR	NR
Low lactose skim milk 1000 ml	6.5 g	NR	18/36 (50%) p <0.025 across groups	NR	NR	NR	NR	NR
Skim milk 125 ml	6.4 g	NR	13/40 (32.5%)	NR	NR	NR	NR	NR
Skim milk 250 ml	12.75 g	NR	18/40 (45%)	NR	NR	NR	NR	NR
Skim milk 500 ml	25.5 g	NR	19/39 (48.7%)	NR	NR	NR	NR	NR
Skim milk 1000 ml	51 g	NR	23/34 (67.6%) p <0.05 across groups	NR	NR	NR	NR	NR
Low lactose whole milk 125 ml	0.63 g	NR	8/40 (20%)	NR	NR	NR	NR	NR
Low lactose whole milk 250 ml	1.25 g	NR	12/40 (30%)	NR	NR	NR	NR	NR
Low lactose whole milk 500 ml	2.5 g	NR	17/40 (42.5%)	NR	NR	NR	NR	NR
Low lactose whole milk 1,000 ml	5 g	NR	21/37 (56.8%) p <0.01 across groups	NR	NR	NR	NR	NR
Whole milk 125 ml	6.1 g	NR	12/38 (31.6%)	NR	NR	NR	NR	NR
Whole milk 250 ml	12.3 g	NR	17/38 (44.7%)	NR	NR	NR	NR	NR
Whole milk 500 ml	24.5 g	NR	21/37 (56.8%)	NR	NR	NR	NR	NR
Whole milk 1,000 ml	49 g	NR	23/36 (63.9%) p <0.05 across groups	NR	NR	NR	NR	NR
Absorbers (n=31)								
Low lactose skim milk 125 ml	0.81 g	NR	7/31 (22.6%)	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Low lactose skim milk 250 ml	1.6 g	NR	8/31 (25.8%)	NR	NR	NR	NR	NR
Low lactose skim milk 500 ml	3.25 g	NR	8/28 (27.6%)	NR	NR	NR	NR	NR
Low lactose skim milk 1000 ml	6.5 g	NR	9/25 (36%) ns (not significant) across groups	NR	NR	NR	NR	NR
Skim milk 125 ml	6.4 g	NR	4/31 (12.9%)	NR	NR	NR	NR	NR
Skim milk 250 ml	12.75 g	NR	5/31 (16.1%)	NR	NR	NR	NR	NR
Skim milk 500 ml	25.5 g	NR	9/31 (29%)	NR	NR	NR	NR	NR
Skim milk 1,000 ml	51 g	NR	10/27 (37%) ns across groups	NR	NR	NR	NR	NR
Low lactose whole milk 125 ml	0.63 g	NR	3/31 (9.7%)	NR	NR	NR	NR	NR
Low lactose whole milk 250 ml	1.25 g	NR	4/30 (13.3%)	NR	NR	NR	NR	NR
Low lactose whole milk 500 ml	2.5 g	NR	9/29 (31%)	NR	NR	NR	NR	NR
Low lactose whole milk 1,000 ml	5 g	NR	8/26 (30.8%) ns across groups	NR	NR	NR	NR	NR
Whole milk 125 ml	6.1 g	NR	2/31 (6.5%)	NR	NR	NR	NR	NR
Whole milk 250 ml	12.3 g	NR	7/31 (22.6%)	NR	NR	NR	NR	NR
Whole milk 500 ml	24.5 g	NR	8/29 (27.6%)	NR	NR	NR	NR	NR
Whole milk 1,000 ml	49 g	NR	9/25 (36%) ns across groups	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Rosado, 1984[133] *Malabsorbers (n=25)*		**Subjects reporting symptoms. A numerical score was given for the presence or absence of 4 symptoms (abdominal cramps, gas/flatulence, vomiting, and/or diarrhea), 0=absent to 3=severe, except for diarrhea which was always marked a 3. Total points were then summed for each of the 3 treatment periods. A score of ≤3 = minor symptoms, ≥4 = major.**						
Lactose prehydrolyzed milk	18 g	NR	24 none 1 minor 0 major	NR	NR	NR	NR	NR
Milk plus Lactaid	18 g	NR	21 none 4 minor 0 major	NR	NR	NR	NR	NR
Milk	18 g	NR	13 none 5 minor 7 major	NR	NR	NR	NR	NR
Absorbers (n=25)								
Lactose prehydrolyzed milk	18 g	NR	24 none 0 minor 1 major	NR	NR	NR	NR	NR
Milk plus Lactaid	18 g	NR	22 none 2 minor 1 major	NR	NR	NR	NR	NR
Milk	18 g	NR	22 none 2 minor 1 major	NR	NR	NR	NR	NR
Haverberg, 1980[126] *Malabsorbers (n=67)*		**Number of subjects reporting GI symptoms during 24 hours after consumption. Occurrence of diarrhea, ≥2 mild GI symptoms or ≥1 moderate or severe symptom was noted as a positive response of intolerance.**						
Lactose free chocolate dairy drink, 240 ml		NR	12 (18%)	NR	NR	NR	NR	NR
Lactose free chocolate dairy drink, 480 ml		NR	15 (22)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 240 ml	10.8 g	NR	19 (28)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 480 ml	21.6 g	NR	26 (39)	NR	NR	NR	NR	NR
Absorbers (n=43)								
Lactose-free chocolate dairy drink, 240 ml		NR	7 (16)	NR	NR	NR	NR	NR
Lactose-free chocolate dairy drink, 480 ml		NR	14 (32)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 240 ml	10.8 g	NR	7 (16)	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lactose-containing chocolate dairy drink, 480 ml	21.6 g	NR	8 (19)	NR	NR	NR	NR	NR
Kwon, 1980[127] *Malabsorbers (n=45 adolescents)*		**Number of subjects reporting GI symptoms during 24 hours after consumption**						
Lactose free chocolate dairy drink, 240 ml		NR	12 (27%)	NR	NR	NR	NR	NR
Lactose free chocolate dairy drink, 480 ml		NR	7 (16)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 240 ml	10.8 g	NR	4 (9)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 480 ml	21.6 g	NR	12 (27)	NR	NR	NR	NR	NR
Absorbers (n=42 adolescents)								
Lactose free chocolate dairy drink, 240 ml		NR	7 (17)	NR	NR	NR	NR	NR
Lactose free chocolate dairy drink, 480 ml		NR	7 (17)	NR	NR	NR	NR	NR
Lactose-containing chocolate dairy drink, 240 ml	10.8 g	NR	8 (19)	NR	NR	NR	NR	NR
Lactose containing chocolate dairy drink, 480 ml	21.6 g	NR	7 (17)	NR	NR	NR	NR	NR
Rorick, 1979[116] *Malabsorbers (n=23)*		**Number of subjects reporting intolerance to test drinks during the afternoon after consumption. Frequency of symptoms is based on only the subjects who reported symptoms, 7 in the malabsorber group, 18 in the absorber group and subjects could be intolerant to both test drinks.**						
Intolerant to only lactose free chocolate dairy drink		NR	2	1 mild *cramps*	4, 3 mild 1 moderate,	6, 3 mild 3 moderate	NA	0
Intolerant to only lactose containing chocolate dairy drink	10.8 g	NR	0	1 mild *cramps*	2, both mild	5, 3 mild 2 moderate	NA	0
Intolerant to both test drinks	0 to 10.8 g	NR	5	Not applicable (NA)	NA	NA	NA	NA
Tolerant to both test drinks	0 to 10.8 g	NR	16	NA	NA	NA	NA	NA
Absorbers (n=64)								
Intolerant to only lactose free chocolate dairy drink		NR	6	1 mild *cramps*	5, 4 mild 1 severe	8, 5 mild 1 moderate 2 severe	NA	1 moderate
Intolerant to only lactose containing chocolate dairy drink	10.8 g	NR	7	1 mild *cramps*	6, 5 mild 1 moderate	10, 7 mild 2 moderate 1 severe	NA	3 mild
Intolerant to both test drinks	0 to 10.8 g	NR	5	NA	NA	NA	NA	NA

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Tolerant to both test drinks	0 to 10.8 g	NR	46	NA	NA	NA	NA	NA
Lisker, 1978[129] *Lactase-deficient subjects (n=97)*		**Number of subjects reporting symptoms. Symptoms were rated according: 1+ if mild; 2+ if moderate; 3+ if marked. Symptoms were scored as severe if diarrhea was present or if a cumulative rating of other symptoms (abdominal cramps, bloating, flatulence) was 4+. Cumulative rating less than 4+ was considered mild.**						
Lactose free milk	0 g	NR	1 mild 96 absent	NR	NR	NR	NR	NR
Regular milk	12.5 g	NR	16 severe 20 mild 61 absent	NR	NR	NR	NR	NR
Regular milk plus additional 25 g lactose	37.5 g	NR	69 severe 12 mild 16 absent	NR	NR	NR	NR	NR
Lactase -sufficient subjects (n=53)								
Lactose free milk	0 g	NR	53 absent	NR	NR	NR	NR	NR
Regular milk	12.5 g	NR	1 severe 1 mild 51 absent	NR	NR	NR	NR	NR
Regular milk plus additional 25 g lactose	37.5 g	NR	2 severe 2 mild 49 absent	NR	NR	NR	NR	NR
Paige, 1975[135] *Lactose malabsorbers (n=22)*		**Number of subjects reporting symptoms during 90 minutes after consumption. Symptoms voluntarily mentioned were recorded. Subjects were not specifically asked if they developed any symptoms commonly associated with lactose intolerance.**						
90% hydrolyzed milk	1.2 g	NR	3	NR	NR	NR	NR	NR
50% hydrolyzed milk	6 g	NR	0 (*n=18*)	NR	NR	NR	NR	NR
Whole milk	12 g	NR	3	NR	NR	NR	NR	NR
Lactose absorbers (n=10)								
90% hydrolyzed milk	1.2 g	NR	0	NR	NR	NR	NR	NR
50% hydrolyzed milk	6 g	NR	0	NR	NR	NR	NR	NR
Whole milk	12 g	NR	0	NR	NR	NR	NR	NR
Jones, 1976, Part I[130] *(n=16)*	**Subjects reporting symptoms of bloating, gas, diarrhea and cramps using scale: 0=no symptoms, 1=mild, 2=moderate, 3=severe, summed**							
Regular skim milk 591.5 ml	30 g	35	15 (93.8%)	NR	NR	NR	NR	NR
50% lactose reduced skim milk 591.5 ml	15 g	17	12 (75%)	NR	NR	NR	NR	NR
75% lactose reduced skim milk 591.5 ml	7.5 g	13	5 (31.3%)	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

B. Prebiotics or probiotics

I. Studies that reported subjects with symptoms at baseline in addition to lactose intolerance by testing

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Newcomer, 1983[144] *(n=18)*	**Mean symptom score over 10wk for diarrhea + pain + gas + borborygmi, averaged and compared to control. *(extracted from graph*)**							
1. 720 ml 2% milk	NR	40	NR	NR	NR	NR	NR	NR
2. 720 ml 2% unfermented acidophilus milk with LA at cell concentration 10^6 cfu/ml	NR	40	NR	NR	NR	NR	NR	NR

II. Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion (based on biochemical measures only)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lin, 1998[117] *(n=20)*	**Mean symptom score over 8 hours, 0-5 from none to severe for abdominal pain, gas and diarrhea averaged and compared to control.**							
1. 400 ml milk with LA at cell concentration 10^8 cfu/ml	20 g	9.8	NR	NR	NR	NR	NR	NR
2. 400 ml milk with LA at cell concentration 10^9 cfu/ml	20 g	6.5 (p<.05)	NR	NR	NR	NR	NR	NR
3. 400 ml of milk with LB at 10^8 cfu/ml	20 g	3.9 (p<.05)	NR	NR	NR	NR	NR	NR
4. 400 ml of milk with L.B at 10^9 cfu/ml	20 g	2.8 (p<.05)	NR	NR	NR	NR	NR	NR
2% milk	20 g	12.5	NR	NR	NR	NR	NR	NR
Mustapha, 1997[139] *(n=11)*	**Subjects rated symptoms (mean ± SEM) on a 0-5 (none to severe) scale for each hour from hour 1 to hour 8 following each of the diets. Diarrhea was monitored 24 hours after diet.**							
Control	15 g	NR	NR	NR	7.44 ± 1.8	9.93 ± 1.73	7.81 ± 2.06	2.69 ± 0.76
ATC 4356 milk (highest B-gal activity)	15 g	NR	NR	NR	5.31 ± 1.18	7.80 ± 1.18	6.71 ± 1.55	1.62 ± 0.63
B Milk	15 g	NR	NR	NR	5.16 ± 1.2	8.68 ± 1.41	6.48 ± 1.22	0.46 ± 0.27 (p<0.05 vs. control)
N1 Milk (lowest B-gal activity)	15 g	NR	NR	NR	5.15 ± 1.39	6.87 ± 1.65 (p<0.05 vs. control)	6.98 ± 2.10	1.08 ± 0.71 (p<0.05 vs. control)
E Milk	15 g	NR	NR	NR	4.57 ± 1.64 (p<0.05 vs. control)	8.40 ± 1.75	5.99 ±1.33	1.31 ± 0.6

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Jiang, 1996[140] *(n=15)*	**Mean ranked scale of symptoms (± SEM) for abdominal pain, flatulence, borborygmi, diarrhea and meteoism: 0=none, 1=slight, 2=mild, 3=moderate, 4=moderately severe, 5= severe summed for hours 1-8. flatus frequency: mean number of gas passages over 8 hours**							
1. 400 ml 2% milk with B.longum B6 from m-MRS broth containing lactose	NR	NR	NR	5.6 ± 1.8	6.0 ± 1.8	7.0 ± 1.7	8.8 ± 2.2	1.8 ± 0.6
2.400 ml 2% milk with B.longum B6 from Sanofi biomed as a concentrated frozen culture	NR	NR	NR	3.8 ±1.5	7.3 ± 2.0	13.2 ± 2.1	8.3 ± 1.7	2.7 ± 1.0
3. 400 ml of bifidus milk with B.longum ATC/C 15708 from m-MRS broth containing lactose	NR	NR	NR	4.4 ± 2.0	6.1 ± 2.6	11.8 ± 2.0	9.6 ± 1.9	2.2 ± 0.6
One meal 400 ml of 2% milk	NR	NR	NR	7 ± 1.8	6.1 ± 2.2	9.2 ± 1.9	9.7 ± 2.0	1.7 ± 0.5
Vesa, 1996[141] *(n=15, results on 14 reported)*	**Ranked scale of symptoms for abdominal pain, flatulence, diarrhea, bloating and sum score: 0=none, 1=mild, 2=moderate, 3=fairly strong, 4=very strong, summed for hours 1-8. Also measured HB post intervention**							
Control: Lactulose 10gm in 250 ml water	18 g	3±0.95	NR	0.42 ±0.19	1.33 ± 0.41	1±0.37	NR	0.25 ± 0.25
1. Ofilus (Yoplait, France; has *L. acidophilus and bifidobacterium*) 320 ml	18 g	1.58±0.76	NR	0.25±0.25	0.58 ± 0.26	0.5±0.36	NR	0.25 ± 0.18
2. Bulgofilus (ofilus bacteria + *L. bulgaricus*) 400 ml	18 g	1.17 ± 0.59 (p<0.05)	NR	0	0.42 ± 0.29 (p<0.05)	0.5±0.34	NR	0.25 ± 0.13
3. Yoplait yogurt 500 ml	18 g	2.17±0.95	NR	0.25±0.18	0.92 ± 0.48	0.5±0.36	NR	0.33 ± 0.19
Lerebours, 1989[142] *(n=16, only 2 with symptoms of LI)*	**Subjects reporting symptoms. No subjects reported diarrhea, pain or flatulence**							
125 g 3x/day of yogurt	18 g	NR	0/8	0	NR	0	NR	0
125 g 3x/day of fermented then pasteurized milk	18 g	NR	0/8	0	NR	0	NR	0
Martini, 1987[143] *(n=16)*	**Subjects reporting gastrointestinal distress symptoms after consuming milk and various yogurts.**							
Unflavored yogurt 455 g	20 g	NR	0/8	0/8	NR	NR	NR	NR
Strawberry flavored yogurt 465 g	20 g	NR	0/9	0/9	NR	NR	NR	NR
Ice milk 410 g	20 g	NR	0/9	0/9	NR	NR	NR	NR
Ice cream 400 g	20 g	NR	0/9	0/9	NR	NR	NR	NR
Unflavored yogurt FY-1 410 g	20 g	NR	0/8	0/8	NR	NR	NR	NR
Unflavored yogurt FY-2 410 g	20 g	NR	0/8	0/8	NR	NR	NR	NR
Unflavored yogurt FY-3 410 g	20 g	NR	0/8	0/8	NR	NR	NR	NR
Whole milk 415 g	20 g	NR	3/8 (38%)	3/8 (38%)	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Savaiano, 1984[145] *(n=9)*	**Subjects reported symptoms after consumption of 2 types of yogurt (regular and pasteurized) and 3 types of milk (regular, sweet acidophilus and buttermilk). Scale not reported.**							
Yogurt 500 gm	20 g	NR	NR	0	NR	0	NR	0
410 g milk	20 g	NR	NR	1	NR	3	NR	1
420 g sweet acidophilus milk	20 g	NR	NR	0	NR	4	NR	3
465 g cultured milk (buttermilk)	20 g	NR	NR	4	NR	8	NR	2
500 g pasteurized yogurt	20 g	NR	NR	0	NR	0	NR	0

C. Other therapies

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Cappello 2005[147]	**Symptoms score referred to the 5 days preceding each evaluation and scored as: 0=absent; 1=mild (awareness of a symptom but easily tolerated); 2=moderate; 3=severe; and 4=very severe at baseline (b), 10 and 40 days (d).**							
Rifaximin x 10 days (n=14)	NA	NR	NR	2.0 ± 1.1 b 0.6 ± 0.7 10d 1 ± 1.2 40d p <0.05 vs. b at 10 and 40d	2.5 ± 1 b 1.6 ± 0.9 10d 1.6 ± 0.9 40d *p <0.05 vs. b at 10 and 40d	NR	2.4 ± 1.1 b 1.4 ± 0.9 10d 1.5 ± 1.2 40d p <0.05 vs. b at 10 and 40d	1.3 ± 1.7 b 0.4 10d 0.2 ± 0.6 40d p <0.05 vs. b at 40d
Placebo x 10 days (n=5)	NA	NR	NR	1.0 ± 1.4 b 1.0 ± 1.4 10d 0.7 ± 0.9 40d	2.8 ± 1.0 b 2.7 ± 0.5 10d 2.7 ± 1.2 40d	NR	1.6 ± 1.3 b 1.5 ± 1.0 10d 1.7 ± 1.7 40d	1.3 ± 1.7 b 1.4 ± 0.9 10d 1.0 ± 0.9 40d
Lactose-free diet x 40 days (n=13)	0 g	NR	NR	1.3 ± 1.0 b 0.7 ± 1.0 10d 0.5 ± 0.7 40d p <0.05 vs. b at 10 and 40d	2.5 ± 1.1 b 1.9 ± 1.3 10d 1.8 ± 1.2 40d p <0.05 vs. b at 10 and 40d	NR	1.8 ± 1.6 b 1.2 ± 1.4 10 d 1.5 ± 1.1 40d* p <0.05 vs. b at 10 and 40d	2.2 b 1.0 ± 0.9 10d 0.7 ± 1.1 40d p <0.05 vs. b at 10 and 40d

Table 19. Occurrence of GI symptoms in randomized trials (continued)

D. Colonic adaptation studies

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Hertzler, 1996[118] *(n=20)*		**Symptoms rating after lactose (L) or dextrose feeding periods (mean ± SEM). The maximum possible score for any individual symptom would be 40 (a *"5"* rating each hour for 8 hours).**						
Dextrose: 0.6 g • kg body wt^{-1} • d^{-1}, then increased by 0.2-g/kg every other day up to a maximum of 1.0 g • kg^{-1} • d^{-1}.		NR	NR	2.3 ± 0.9	NR	8.1 ± 1.6 p=0.25 vs. L	*Flatulence frequency (n=6)* 23 ± 2.8 p=0.028 vs. L	1.4 ± 0.6
Lactose: 0.6 g • kg body wt^{-1} • d^{-1}, then increased by 0.2-g/kg every other day up to a maximum of 1.0 g • kg^{-1} • d^{-1}.		NR	NR	2.6 ± 0.9	NR	4.5 ± 1.0	11 ± 2.6	1.6 ± 0.6
Briet , 1997[146] *(n=46)*		**Every hour, subjects reported any occurrence of abdominal pain, borborygmus, flatulence, and abdominal distension, and graded each symptom$_5$ as absent = 0, mild = 1, moderate = 2, or severe = 3. The total clinical score was calculated for each subject by summing the scores for each symptom (range 0 to 144).**						
Sucrose 17 g plus 50 g aspartame (to mask taste) twice daily (34 g sucrose total) over 13 days (days 2 to 14).		24.2 ± 12.8	NR	NR	NR	NR	NR	NR
Lactose 17 g plus 50 g aspartame (to mask taste) twice daily (34 g lactose total) over 13 days (days 2 to 14).		20.2 ± 13.9 p=ns between groups	NR	NR	NR	NR	NR	NR

E. Incremental lactose load studies or studies examining different levels of lactose

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Hertzler, 1996[119] *(n=13)*		**Symptoms rating (mean ± SEM) after lactose (L) or dextrose feeding periods. The maximum possible score for any individual symptom would be 40 (a *"5"* rating each hour for 8 hours).**						
Lactose (dissolved in 240 ml water)	0 g	NR	NR	1.7 ± 0.8	NR	3.4 ± 1.0	*Flatulence frequency* 4.0 ± 1.3	1.1 ± 0.9
Lactose	2 g	NR	NR	1.7 ± 0.9	NR	3.8 ± 1.4	4.3 ± 1.8	1.0 ± 0.8
Lactose	6 g	NR	NR	1.2 ± 0.5	NR	1.9 ± 0.9	5.1 ± 0.6	0.2 ± 0.2
Lactose	12 g	NR	NR	3.4 ± 0.8	NR	3.5 ± 1.3	4.6 ± 1.1	1.2 ± 0.9
Lactose	20 g	NR	NR	5.3 ± 1.8	NR	6.6 ± 1.8	9.0 ± 2.6	1.8 ± 1.2
		Symptom ranking (mean ± SEM) after lactose (L) or dextrose feeding periods. Treatments were ranked 1 (least symptoms) through 5 (most symptoms).						
Lactose (dissolved in 240 ml water)	0 g	NR	NR	2.4 ± 0.3	NR	2.7 ± 0.3	*Flatulence frequency* 2.7 ± 0.6	2.9 ± 0.2

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lactose	2 g	NR	NR	2.5 ± 0.2	NR	3.0 ± 0.3	2.5 ± 0.4	2.9 ± 0.2
Lactose	6 g	NR	NR	2.4 ± 0.2 p≤0.05 for 0-6 g vs. 12 and 20 g	NR	1.9 ± 0.2 p≤0.05 vs. 2, 12, 20 g	2.4 ± 0.3	2.7 ± 0.2
Lactose	12 g	NR	NR	3.8 ± 0.3	NR	3.2 ± 0.4	3.2 ± 0.4	2.5 ± 0.2
Lactose	20 g	NR	NR	3.9 ± 0.3	NR	4.2 ± 0.3 p≤0.05 vs. all other treatments	4.3 ± 0.3 p≤0.05 vs. all other treatments	3.5 ± 0.3
Newcomer, 1978[120] *(n=59)*	**Number of subjects reporting symptoms. A subject was considered to have a positive symptomatic response if he/she had ≥1 loose stools or had a grade 2+ or higher in at least one of the following symptoms: abdominal cramps/pain, bloating or gas, borborygmi, flatulence. 1+=slight; 2+=mild; 3+=moderate; 4+=severe.**							
Breakfast 1	0 g	NR	56 ≤+1 3 ≥+2 (1 +3)	NR	NR	NR	NR	0
Breakfast 2	3 g	NR	57 ≤+1 2 ≥+2 (1 +4)	NR	NR	NR	NR	1
Breakfast 3	6 g	NR	53 ≤+1 6 ≥+2 (1 +4)	NR	NR	NR	NR	2
Breakfast 4	9 g	NR	52 ≤+1 7 ≥+2 (1 +3, 1 +4)	NR	NR	NR	NR	2
Breakfast 5	12 g	NR	56 ≤+1 3 ≥+2 (1 +4)	NR	NR	NR	NR	1
Breakfast 6	18 g	NR	56 ≤+1 3 ≥+2 (1 +3, 1 +4)	NR	NR	NR	NR	1
Stephenson, 1974[131] *(n=16 LI subjects that got symptoms with 50 g lactose in water test dose)*	**Subjects reporting symptoms of diarrhea, gas, bloating and cramps according to scale: 1=mild, 2=moderate, 3= severe summed for the 4 symptoms**							
Lactose in water	15 g	NR	7%	NR	NR	NR	NR	NR
Lactose in water	30 g	NR	58%	NR	NR	NR	NR	NR
Lactose in water	50 g	NR	14%	NR	NR	NR	NR	NR
Lactose in milk	15 g	NR	20%	NR	NR	NR	NR	NR

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Lactose in milk	30 g	NR	66%	NR	NR	NR	NR	NR
Lactose in milk	50 g	NR	7%	NR	NR	NR	NR	NR
Lactose in water	100 g	NR	14%	NR	NR	NR	NR	NR
Lactose in water	150 g	NR	7%	NR	NR	NR	NR	NR
Lactose in water	200 g	NR	0	NR	NR	NR	NR	NR
Lactose in milk	100 g	NR	7%	NR	NR	NR	NR	NR
Lactose in milk	150 g	NR	0	NR	NR	NR	NR	NR
Lactose in milk	200 g	NR	0	NR	NR	NR	NR	NR
Stephenson, 1974[131] *(n=19 lactose tolerant subjects that did not get symptoms with 50 g lactose in water test dose)*	**Subjects reporting symptoms of diarrhea, gas, bloating and cramps according to scale: 1=mild, 2=moderate, 3= severe summed for the 4 symptoms**							
Lactose in water	15 g	NR	0	NR	NR	NR	NR	NR
Lactose in water	30 g	NR	5%	NR	NR	NR	NR	NR
Lactose in water	50 g	NR	16%	NR	NR	NR	NR	NR
Lactose in milk	15 g	NR	0	NR	NR	NR	NR	NR
Lactose in milk	30 g	NR	13%	NR	NR	NR	NR	NR
Lactose in milk	50 g	NR	6%	NR	NR	NR	NR	NR
Lactose in water	100 g	NR	21%	NR	NR	NR	NR	NR
Lactose in water	150 g	NR	32%	NR	NR	NR	NR	NR
Lactose in water	200 g	NR	26%	NR	NR	NR	NR	NR
Lactose in milk	100 g	NR	31%	NR	NR	NR	NR	NR
Lactose in milk	150 g	NR	31%	NR	NR	NR	NR	NR
Lactose in milk	200 g	NR	19%	NR	NR	NR	NR	NR

F. Studies with IBS subjects

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Parker, 2001[175] *(n=33 IBS subjects, only 23 completed 3 weeks of low lactose diet. 7 of 9 of subjects improving on the diet were double-blind, placebo-controlled challenges*		**Symptom score based on eight variables: abdominal pain, number of daily bowel movements, urgency to defecate, consistency of feces, flatulence, headache, abdominal distension and general well-being. Each symptom, except urgency, was scored from 0 to 4, with 0 being no symptoms and 4 being most severe. Urgency was scored from 0 to 3. The maximum cumulative score was 31.**						
Lactose challenges	0 to 15 g	During the double blind, placebo controlled challenges, two of the seven (29%) showed worsening symptoms with higher levels of lactose. The remaining five were inconclusive but 5/7 (71%) had worsening symptoms with 15 g of lactose						

Table 19. Occurrence of GI symptoms in randomized trials (continued)

Study (n) / Interventions	Lactose Content/ Day	Overall Symptom Score	Number of Subjects Reporting Symptoms	Abdominal Pain/Cramps	Abdominal Bloating	Flatulence	Borborygmi (*or other*)	Diarrhea
Böhmer, 1996[176] *(n=70 IBS subjects total)*		**Cumulative score with a total score of 18. Subjects scored symptoms (pain, flatulence, distension, diarrhea, mucus, incomplete evacuation) from 0=no complaints, 1=mild; 2=moderate; and 3 as severe. A maximum.**						
Lactose malabsorbers based on hydrogen breath test (n=17)								
Baseline score	19.1	13.6						
3 weeks after lactose restricted diet	<9 g	7.3 (p<0.001 vs. baseline						
6 weeks after lactose restricted diet	<9 g	4.2 (p<0.001 vs. baseline						
Lactose absorbers based on hydrogen breath test (n=53)								
Baseline score	19.1	13.1						
3 weeks after lactose restricted diet	<9 g	11.6						
6 weeks after lactose restricted diet	<9 g	11.8						
Lisker, 1989[177] *(n=12, 8 were lactose nonpersistent based on hydrogen breath test)*		**Diary record of symptoms filled out daily. Symptoms included constipation, diarrhea, abdominal pain, abdominal distension, and flatulence.**						
Placebo or hydrolyzed milk		IBS symptoms appeared to be independent of lactose malabsorption following 3 months of treatment						
Newcomer, 1983[144] *(n=89 total)*		**Symptom (diarrhea, abdominal pain/cramps, gas/flatus, rumbling, constipation) diary at end of each day. Scored as following: 0=no trouble; 1=slight trouble; 2=mild; 3=moderate; 4=severe. Constipation was better, same, worse. Diarrhea was yes/no, # stools per day.**						
Lactase deficient group (n=18)								
Unaltered milk	NR, mean 1½ glasses/d	There was no significant difference in symptoms during the acidolphilus and unaltered milk periods. Intestinal symptoms increased significantly with both acidolphilus and unaltered milks compared to the control (no milk) period.						
Acidolphilus milk	NR, mean 1½ glasses/d							
IBS group (n=61)								
Unaltered milk	NR, mean 1½ glasses/d	Symptoms were not helped by the ingestion of acidophilus milk.						
Acidolphilus milk	NR, mean 1½ glasses/d							

Chapter 4. Discussion

Summary and Discussion

Our evidence synthesis has the following major conclusions: (1) Reliable estimates of U.S. prevalence rates for LI are not currently available, though there is some evidence that the magnitude of LI will be very low in young children and remain low into adult ages for most populations of Northern European descent. For African American, Hispanic, Asian, and American Indian populations the rates of LI will likely be higher in late childhood and adulthood. (2) Evidence regarding the effect of dairy exclusion diets on long-term GI and bone health outcomes is relatively sparse in quantity and low in quality. The evidence does not strongly indicate that dairy free diets are independently associated with poor long-term bone health outcomes, and there is no direct information on long-term GI outcomes among individuals consuming dairy free diets. However, results from genetic association tests consistently reported decreased consumption of milk in adults with the C/C genotype compared to those with at least one T allele, suggesting that individuals with lactase nonpersistence avoid milk presumably to reduce dairy induced GI symptoms. (3) The majority of symptomatic individuals diagnosed with LI can likely tolerate up to 12 grams (equivalent of 1 cup of milk) at a given setting with minimal to no symptoms, especially if consumed with other foods. (4) Although reduced lactose consumption is logical and a biologically plausible treatment plan, evidence was insufficient to determine if lactose reduced milk products result in clinically important improvements in GI symptoms in individuals diagnosed with LI who wish to consume doses of lactose that exceed 12 grams per serving. There was also insufficient evidence on the effects of other treatment options, including probiotics and incremental lactose loads.

Our findings have important research and clinical implications. With regard to LI prevalence estimates, most of the identified research assessed subjective symptoms in an unblinded fashion, an inability of individuals to fully absorb lactose, irrespective of symptoms or lactase nonpersistence. Data available tended to be from highly selected populations and not likely representative of the overall U.S. population. Racial and ethnic variation was clearly present, but the variation in symptoms reported following a challenge does not seem as extreme as the racial and ethnic variation seen in lactose malabsorption and prevalence of hypolactasia. This is likely due in part to the fact the GI symptoms are commonly caused by factors unrelated to LI, so the effects due to lactose are likely attenuated by symptoms caused by nonlactose factors. Also, many people who malabsorb lactose do not report symptoms. Additional genetic association studies may provide a useful method to assess LI in epidemiologic studies. Dietary history assessing dairy consumption and symptoms linked to results from testing for the lactase gene might obviate the need for blinding of lactose intake.

Dietary lactose intake and supplemental calcium consumption were recorded in a few observational studies. We found inconsistent increased risk of bone fracture in populations with documented or assumed low lactose intake. Poor documentation of dietary intake may contribute to inconsistency in results of observational studies. A recently published systematic review of the association between vitamin D and dietary calcium also found that inconsistent dietary analysis hampered synthesis of evidence.[179] The authors could not find consistent evidence that increased dietary or supplemental vitamin D and calcium intake improves bone health. Because the major

Appendixes and evidence tables cited in this report are available at http://www.ahrq.gov/downloads/pub/evidence/pdf/lactoseint/lactint.pdf.

long-term health concern of dairy exclusion diets beyond GI symptoms is the potential for intake of calcium below recommended dietary levels, future research is needed to accurately assess long-term bone health outcomes in populations that consume dairy free diets. We found that dairy interventions in healthy children with low baseline milk intake may result in short but not long-term improvement of bone mineral content and density. Adults with lactose free or low lactose diet may have increased risk of bone fractures. Low and inconsistent evidence suggested that adults with milk intolerance and malabsorption had greater odds of fractures and worse bone outcomes. Adult women with low childhood and lifetime milk intake, LM, and C/C genotype had greater risk of osteoporosis and fractures. However, studies did not find significant association with lactose metabolism and bone health in men. There was little data on African Americans. Additional information would be important because African Americans have a higher prevalence of LI, likely lower consumption of dairy products, yet have lower rates of bone health outcomes of interest for this report. Children with low baseline calcium consumption may benefit from increased lactose intake. It is not clear if increased milk consumption in healthy adult women with low childhood and lifetime milk intake, LM, or C/C genotype reduces the risk of osteoporosis and fractures.

Our findings can aid patients and practitioners in clinical management of individuals diagnosed with LI. The preponderance of evidence indicates individuals diagnosed with LI can be informed that they can ingest 12 grams of lactose (one cup of milk) as a single dose (particularly if taken with food) with no or minor symptoms. Therefore, most individuals diagnosed (either self or clinically), can consume a sufficient amount of dairy products each day to meet minimum recommendations without incurring GI symptoms. However, as the dose is increased above 12 grams, these individuals can be informed that intolerance becomes more prominent, with single doses of 24 grams usually yielding appreciable symptoms. There is some evidence that if 24 grams of lactose is distributed throughout the day, many lactose malabsorbers will tolerate this dosage. Lactose in a dose of 50 grams induces symptoms in the vast majority of subjects. No studies assessed if lactose malabsorbers of differing ethnicities have differing tolerance to lactose. There was no data on the relationship of age or sex to the quantity of lactose that can be tolerated.

Advice regarding additional management strategies is hampered from the lack of study uniformity in design and methodology. For individuals with LI who wish to consume more than 12 grams of lactose at an individual sitting, there is insufficient evidence of clinically relevant reductions in overall symptoms and abdominal pain and diarrhea with consumption of lactose reduced milk (to content of 0-2 grams). However, we caution that the criterion of being symptomatic at baseline was found only in a few studies, and not all of the enrolled subjects may have actually been lactose intolerant. This greatly reduces the applicability of these studies to the clinical management of individuals with LI as well and limits the comparison of findings across studies. Most studies had an 8-hour recording period, and it is difficult to generalize these findings to individuals with chronic relapsing remitting problems with a constellation of symptoms. Individuals can be informed that while some studies indicated that treatments provided a statistical benefit, symptomatic improvement generally went from none to mild or slight, and the clinical significance for many individuals may be low. There is little information on the effect of these interventions on diarrhea and abdominal pain.

Key Question 5: What are the future research needs for understanding and managing lactose intolerance?

Key Question 1

In order to accurately assess the population prevalence of lactose, future studies will need to be derived from population based samples that include adequate distributions across ages and ethnic variation in order to map the effects of these important factors. Effort will also need to be made to account for possible placebo effects in reporting symptoms. The best mechanisms available for accounting for placebo effects would be to conduct blinded challenges with and without lactose and to assign the difference in reported symptoms and the true prevalence due to the lactose challenge. Additional work on what constitutes a meaningful challenge dose should also be conducted. For the research to be clinically meaningful, research on LI should take into account the prevalence of symptoms that might be expected following doses of lactose that would be consumed during a normal diet as compared to extreme doses of lactose that are comparable to getting a recommended daily intake of calcium from a one-time consumption of milk.

Key Question 2

We were unable to identify long-term studies that assess the impact of dairy exclusion diets on GI symptoms, especially if blinding individuals to dairy exclusion. Studies evaluating individuals diagnosed with IBS and gluten intolerance are needed. Future research should investigate the association between dietary calcium and patient outcomes in patients with LI and lactose free diets. The target populations for investigational research should include children, elderly, gender and ethnic subgroups, and patients with genetic polymorphism. The sources of dietary calcium from nondairy products and from nutritional supplements should be examined separately and in interaction with other dietary patterns (food synergy).[148-150] Despite the widespread perception that low intake of dairy products and associated low vitamin D and calcium intake can lead to poor health outcomes, bone health in patients with LI is unknown. Length and doses of dairy products, probiotics, and plant calcium sources, as well as patient adherence to the recommended treatment regimes, may modify the association and should be examined in future research. Future research should prioritize patient outcomes, including bone fractures and intermediate outcomes of bone density and mineral content. Other health outcomes, including obesity, diabetes, cardiovascular diseases, and cancer, should be examined in treated and untreated lactose intolerant patients in comparison with the general population. In children with LI, incidence of infection and allergic diseases should be evaluated in long-term observational studies and in randomized controlled clinical trials of available treatment options.

Key Question 3

Future research needs to examine if lactose malabsorbers of differing ethnicities have differing tolerance to lactose. Additionally, blinded RCTs should enroll and provide outcomes among subjects according to age and gender to determine if the quantity of lactose that can be tolerated by lactose intolerant subjects varies by these characteristics. Reporting of outcomes in a standardized

validated fashion and determining clinically significant as well as statistically significant differences are needed.

Key Question 4

Few studies have tested the hypotheses that incremental lactose loads for colonic adaptation is beneficial. Furthermore, studies that have examined different products to prevent LM used a wide variety of patients, interventions, comparisons, and outcomes. Pooling results is difficult, and determining generalized estimates of clinically relevant effect sizes was generally not feasible. Future research is needed employing standardized interventions with blinded controls and reported validated outcomes in a standardized fashion.

In summary, while probiotics, lactose reduced milks, and lactase supplements hold great promise and high public acceptance, evidence of efficacy and effectiveness in specific populations is lacking. Rigorous scientific data to support their use is lacking, and there is also a dearth of information on their safety. Probiotics are generally considered effective and safe. Using the approach, “they can’t hurt and may help” is potentially erroneous as safety and efficacy, particularly long-term use, are not known.

The connection between bench and bedside application needs to be made. A large body of literature exists on physiological and experimental measurement of LM, but few studies evaluate the symptomatic response of agents. Also, the correlation between measurement of hydrogen breath excretion, colonic bacterial fermentation, and lactase activity and other physiological measurements with symptomatic improvement needs to be studied and reported.

Need for blinded randomized clinical studies. LI is well recognized by the medical and lay community and is often blamed for being the cause of diarrhea, abdominal pain, bloating, and flatulence. Patients self diagnose the condition and drastically reduce or stop their intake of lactose or use supplements to help digest lactose. This has the variable effect of reducing or alleviating symptoms. However, given the subjective nature of symptoms and the large placebo effect of any dietary manipulation, it is unclear if the response is a ‘placebo effect’ or due to use of supplements. The literature on efficacy of hydrolyzed milk, probiotics, and supplements to help digest lactose is fraught with this problem. Rigorous double blinded placebo controlled studies are required to demonstrate efficacy, and larger long-term studies demonstrating effectiveness are needed. There also needs to be rigorous long-term safety data of these agents. Outcomes reported in a standardized validated fashion and that determine clinically significant as well as statistically significant differences are needed.

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(Note that this set of references is different from those in Appendix D and the numbers are different.)

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List of Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
CaMos	Canadian Multicentre Osteoporosis Study
CH_4	Methane
CI	Confidence interval
Co_2	Carbon dioxide
DOES	Dubbo Osteoporosis Epidemiology Study
EPC	Evidence-based Practice Center
EPIC	European Prospective Investigation into Cancer and Nutrition
EPOS	European Prospective Osteoporosis Study
EVOS	European Vertebral Osteoporosis Study
g	Gram
GI	Gastrointestinal
GRADE	Grades of Recommendation Assessment, Development, and Evaluation
H_2	Hydrogen gas
IBS	Irritable bowel syndrome
kg	Kilogram
L	Liter
LCT	Lactase gene
LI	Lactose intolerance
LM	Lactose malabsorption
mg	Milligram
ml	Milliliter
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
OMAR	Office of Medical Applications of Research
OR	Odds ratio
ppm	Parts per million
RCT	Randomized controlled trial
SNP	Single nucleotide polymorphism
TEP	Technical Expert Panel

Appendix A. Technical Expert Panel Members and Affiliation

TEP Member	Affiliation
Melvin Heyman, MD	School of Medicine University of California San Francisco, California
Jay Perman, MD	College of Medicine Chandler Medical Center Lexington, Kentucky
Frederick Suchy, MD	Pediatric Gastroenterology Mount Sinai Hospital New York, New York

Appendix B. Search Strings

Q1

Database: Ovid MEDLINE(R)
Search Strategy:

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1 lactose intoleran*.mp. or exp Lactose Intolerance/ (2726)
2 milk intoleran*.mp. (286)
3 lactose malabsor*.mp. (493)
4 exp Lactase/ or lactase deficien*.mp. (961)
5 prevalen*.mp. or exp Prevalence/ (325492)
6 exp Population/ or population.mp. (682952)
7 exp Lactose Tolerance Test/ (313)
8 4 or 1 or 3 or 7 or 2 (3490)
9 6 or 5 (914652)
10 8 and 9 (515)
11 exp Cohort Studies/ (694867)
12 11 or 5 (980226)
13 8 and 12 (424)
14 limit 13 to (english language and humans) (365)
15 remove duplicates from 14 (362)

Q2

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp Lactose Intolerance/dh [Diet Therapy] (185)
2 limit 1 to english language (131)
3 exp epidemiologic studies/ (1121620)
4 3 and 2 (12)
5 (lactose restricted or lactose free).mp. (242)
6 dairy exclusion.mp. (0)
7 dairy free.mp. (9)
8 7 or 5 (251)
9 8 and 3 (36)
10 limit 9 to english language (28)
11 4 or 10 (35)

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp lactose/df (9)
2 hypolactas$.mp. (181)
3 (lactose adj2 free).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (273)
4 (dairy adj2 free).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (42)
5 (dairy adj2 exclu$).mp. (12)
6 low lactose.mp. (123)
7 limited lactose.mp. (2)
8 (lactose adj2 restrict$).mp. (38)
9 (dairy adj2 restrict$).mp. (19)
10 exp Lactose Intolerance/ (2478)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (2902)
12 exp Diet/ (144995)
13 dh.fs. (29635)
14 diet$.mp. (372626)
15 13 or 12 or 14 (405928)
16 11 and 15 (933)
17 exp Bone Density/ (28018)
18 exp "Bone and Bones"/ (382334)
19 exp Osteoporosis/ (33396)
20 exp Fractures, Bone/ (108442)
21 exp Bone Diseases/ (318865)
22 21 or 18 or 19 or 17 or 20 (653576)
23 22 and 16 (51)
24 exp Treatment Outcome/ (371740)
25 "Outcome and Process Assessment (Health Care)"/ (16843)
26 outcome$.mp. (801020)
27 25 or 24 or 26 (813119)
28 27 and 16 (45)
29 ep.fs. (828160)
30 exp Epidemiologic Studies/ (1087836)
31 exp Epidemiologic Methods/ (2978476)
32 30 or 31 or 29 (3265926)
33 32 and 16 (290)
34 33 or 28 or 23 (341)
35 limit 34 to (english language and humans) (298)
36 limit 35 to journal article (293)
37 limit 35 to (case reports or comment or editorial or letter or "review") (66)
38 36 not 37 (232)

MEDLINE® via Pubmed

Search "Diet, Vegetarian"[Mesh] AND calcium Limits: Humans, Journal Article, English	158
Search "Diet, Vegetarian"[Mesh] AND relative risk AND dairy Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	20
Search "Diet, Vegetarian"[Mesh] AND relative risk Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	279
Search "Diet, Vegetarian"[Mesh] AND lactose Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	4
Search "Diet, Vegetarian"[Mesh] AND lactose free Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	0
Search "Diet, Vegetarian"[Mesh] AND cancer Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	156
Search "Diet, Vegetarian"[Mesh] AND bone Limits: Humans, Journal Article, English, All Adult: 19+ years, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	46
Search avoidance AND "Calcium, Dietary"[Mesh] AND "Dairy Products"[Mesh] Limits: Humans, Journal Article, English	8
Search intolerance AND "Calcium, Dietary"[Mesh] AND "Dairy Products"[Mesh] Limits: Humans, Journal Article, English	35
Search "Calcium, Dietary"[Mesh] AND "Dairy Products"[Mesh] Limits: Humans, Journal Article, English	517
Search "Calcium, Dietary"[Mesh] AND relative risk AND lactose intolerance Limits: Humans, Journal Article, English	22

Scirus

1-10 of 23 hits for"Lactose-free diet" (fracture)

Q3

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp epidemiologic studies/ (1121620)
2 exp lactose intolerance/ (2583)
3 exp Lactose Tolerance Test/ (329)
4 3 and 2 (268)
5 1 and 4 (19)
6 limit 5 to english language (18)
7 exp lactose/ad (469)
8 7 and 2 (117)
9 8 and 1 (13)
10 limit 9 to english language (13)
11 6 or 10 (27)
12 lactose intake.mp. (63)
13 1 and 12 and 2 (8)
14 limit 13 to english language (6)
15 11 or 14 (30)

Q4

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp epidemiologic studies/ (1121620)
2 exp Lactose Intolerance/dh, su, dt, th [Diet Therapy, Surgery, Drug Therapy, Therapy] (413)
3 1 and 2 (20)
4 limit 3 to english language (16)
5 exp lactose intolerance/ (2583)
6 limit 5 to "therapy (optimized)" (114)
7 1 and 6 (11)
8 limit 7 to english language (11)
9 4 or 8 (24)

MEDLINE® via Pubmed

"Probiotics"[Mesh] AND "lactose intolerance" Limits: Humans, Journal Article, English probiotics 45
Search lactose-free AND "lactose intolerance" Limits: Humans, Journal Article, English 55

Q5

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Lactose Intolerance/ (2583)
2 td.fs. (203594)
3 1 and 2 (4)
4 from 3 keep 1 (1)
5 future research.mp. (21817)
6 research need$.mp. (2549)
7 trend$.mp. (147898)
8 1 and 5 (2)
9 6 and 1 (0)
10 1 and 7 (14)
11 8 or 4 or 10 (17)
12 from 11 keep 1-2,11-13 (5)
13 further investigation.mp. (26459)
14 1 and 13 (6)
15 from 14 keep 2,4-5 (3)
16 12 or 15 (7)
17 understanding.mp. (243623)
18 1 and 17 (14)
19 from 18 keep 1,3 (2)
20 from 18 keep 1,3,6-11,13 (9)
21 19 or 16 or 20 (16)

The broader preliminary literature search in MEDLINE® via Pubmed can be summarized as follows:

Relevant MeSH terms	Number identified
"Lactose Intolerance"[Mesh]	2461
"Lactose Intolerance"[Mesh] NOT review NOT comment Limits: Humans, Journal Article, English	1355
"Lactose Intolerance"[Mesh] AND "Epidemiologic Studies"[Mesh] Limits: Humans, English	122
"Lactose Intolerance"[Mesh] Limits: Humans, Randomized Controlled Trial, English	84

Additionally, the Cochrane Central Register of Controlled Trials (CENTRAL) was searched using the terms “lactose OR lactase”, which yielded 792 references.

Appendix C. List of Excluded Studies

1. Lactase deficiency. N Engl J Med 1965 Nov 11; 273(20):1108-9. *Not relevant to key questions*
2. Synthetic foods and deficiency states. Lancet 1965 Nov 6; 2(7419):937-8. *Not relevant to key questions*
3. Primary intestinal lactase deficiency. Nutr Rev 1967 Sep; 25(9):265-70. *Not relevant to key questions*
4. Recurrent abdominal pain. Pediatrics 1970 Dec; 46(6):968-75. *Not relevant to key questions*
5. Correspondence re iron fortified formulas. Pediatrics 1971 Jul; 48(1):152-6 passim. *Not relevant to key questions*
6. Background information on lactose and milk intolerance. A statement of the Food and Nutrition Board Division of Biology and Agriculture, National Research Council. Nutr Rev 1972 Aug; 30(8):175-6. *Review*
7. Lactose intolerance in Greeks. Lancet 1973 Feb 17; 1(7799):367-8. *Not relevant to key questions*
8. American Academy of Pediatrics Committee on Nutrition. Should milk drinking by children be discouraged? Pediatrics 1974 Apr; 53(4):576-82. *Not relevant to key questions*
9. Editorial: Lactase deficiency. Lancet 1975 Nov 8; 2(7941):910-1. *Editorial*
10. Editorial: When does lactose malabsorption matter in adults? Br Med J 1975 May 17; 2(5967):351-2. *Editorial*
11. Soy-based formulas for infants. Med Lett Drugs Ther 1976 Nov 19; 18(24):104. *Not relevant to key questions*
12. The lactose intolerance test and milk consumption. Nutr Rev 1976 Oct; 34(10):302-4. *Not relevant to key questions*
13. Clinical case presentation: diarrhea following tube feeding. JPEN J Parenter Enteral Nutr 1978; 2(1):41-2. *Not relevant to key questions*
14. From the NIH: Recurrent abdominal pain in a healthy school-aged child can be lactose intolerance. JAMA 1979 Dec 14; 242(24):2670. *Not relevant to key questions*
15. Metabolic bone disease as a result of lactase deficiency. Nutr Rev 1979 Mar; 37(3):72-3. *Comment*
16. Efficacy and indications of ursodeoxycholic acid treatment for dissolving gallstones. A multicenter double-blind trial. Tokyo Cooperative Gallstone Study Group. Gastroenterology Vol 78; 1980: 542-8. *Not lactose intolerance study*
17. Treatment of lactose intolerance. Med Lett Drugs Ther 1981 Jul 24; 23(15):67-8. *Not relevant to key questions*
18. Soy-protein formulas: recommendations for use in infant feeding. Pediatrics 1983 Sep; 72(3):359-63. *Not relevant to key questions*
19. Nonpharmacological approaches to the control of high blood pressure. Final report of the Subcommittee on Nonpharmacological Therapy of the 1984 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 1986 May; 8(5):444-67. *Guideline*
20. American Academy of Pediatrics Committee on Nutrition: Practical significance of lactose intolerance in children: supplement. Pediatrics 1990 Oct; 86(4):643-4. *Not relevant to key questions*

21. Evaluation of an algorithm for the treatment of persistent diarrhoea: a multicentre study. International Working Group on Persistent Diarrhoea. Bulletin of the World Health Organization 1996; 74(5):479-89. *Not relevant to key questions*
22. More lactose in your life? Health News 1999 Jan 5; 5(1):6. *Not relevant to key questions*
23. Milk: got proof? We assess the evidence behind the dairy industry's ads and critics' claims. Consum Rep 2001 Sep; 66(9):62-3. *Not relevant to key questions*
24. Information from your family doctor. Lactose intolerance. Am Fam Physician 2002 May 1; 65(9):1855-6. *Not relevant to key questions*
25. Probiotics: using bacteria to improve health. Harv Health Lett 2002 Mar; 27(5):1-3. *Not relevant to key questions*
26. Why milk matters: questions and answers for professionals. Nutr Clin Care 2003 Oct-Dec; 6(3):140-2. *Review*
27. Got milk? No thanks! Up to 20% of Americans believe they're lactose intolerant. Just how intolerant varies with the person and the food. Harv Health Lett 2003 Dec; 29(2):6-7. *Not relevant to key questions*
28. Position of the American Dietetic Association and Dietitians of Canada: vegetarian diets. Can J Diet Pract Res 2003 Summer; 64(2):62-81. *Guideline*
29. Asthma inhalers may pose risks in the milk-allergic child. Child Health Alert 2005 Jan; 23:1-2. *Not relevant to key questions*
30. Lactose intolerance in children and adolescents. Child Health Alert 2006 Oct; 24:3. *Not relevant to key questions*
31. I love milk, but I notice that as I get older I seem to tolerate it less--experiencing gas and bloating. Is this normal? Mayo Clin Womens Healthsource 2006 May; 10(5):10. *Not relevant to key questions*
32. Aalberts JS, Weegels PL, van der Heijden L, et al. Calcium supplementation: effect on blood pressure and urinary mineral excretion in normotensive male lactoovovegetarians and omnivores. Am J Clin Nutr 1988 Jul; 48(1):131-8. *Not eligible outcomes*
33. Abate G, Taormina F, Brillante C, et al. [The effects of the carbocalcitonin + arginine-lysine-lactose combination in senile involutional osteoporosis]. Minerva medica Vol 85; 1994: 253-9. *Not lactose intolerance study*
34. Abbas H. A genetic study of lactose digestion in Pakistani families. Indian J Med Sci 1984 Jul; 38(7):129-33. *Not relevant to key questions*
35. Abbas H. Primary adult hypolactasia. J Pak Med Assoc 1985 Feb; 35(2):55-7. *Not relevant to key questions*
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38. Abdo-Bassols F, Lifshitz F, Del Castillo ED, et al. Transient lactose intolerance in premature infants. Pediatrics 1971 Nov; 48(5):816-21. *Not relevant to key questions*
39. Abdulla M. Public health/clinical significance of inorganic chemical elements. Experientia Suppl 1983; 44:339-55. *Not eligible outcomes*
40. Abdulla M, Andersson I, Asp NG, et al. Nutrient intake and health status of vegans. Chemical analyses of diets using the duplicate portion sampling technique. Am J Clin Nutr 1981 Nov; 34(11):2464-77. *Not relevant to key questions*

41. Abelow BJ, Holford TR, Insogna KL. Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. Calcif Tissue Int 1992 Jan; 50(1):14-8. *Secondary data analysis*
42. Abraham G, Varsha P, Mathew M, et al. Malnutrition and nutritional therapy of chronic kidney disease in developing countries: the Asian perspective. Adv Ren Replace Ther 2003 Jul; 10(3):213-21. *Review*
43. Abraham JM, Levin B, Oberholzer VG, et al. Glucose-galactose malabsorption. Arch Dis Child 1967 Dec; 42(226):592-7. *Not relevant to key questions*
44. Abramowitz A, Granot E, Tamir I, et al. Two-hour lactose breath hydrogen test. J Pediatr Gastroenterol Nutr 1986 Jan; 5(1):130-3. *Not relevant to key questions*
45. Abrams SA, Griffin IJ, Davila PM. Calcium and zinc absorption from lactose-containing and lactose-free infant formulas. The American journal of clinical nutrition Vol 76; 2002: 442-6. *Not lactose intolerance*
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86. Andiran F, Dayi S, Mete E. Cows milk consumption in constipation and anal fissure in infants and young children. J Paediatr Child Health 2003 Jul; 39(5):329-31. *Not relevant to key questions*
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Appendix D. Evidence Tables

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Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes

Study	Subjects	Diagnosis and Control for Bias	Comments
Alhava, 1977[1] Country: Finland Population: Adults Source: The Outpatient Clinic in the University of Central Hospital, Kuopio Study design: Cross-sectional	Inclusion: Adults with documented positive lactose intolerance test and healthy controls Exclusion: General malabsorption, rheumatoid arthritis, other diseases that affect bone metabolism Excluded: NS Inclusion age: >19 Followup: None Mean age: 21-72 for men and 19-71 for women	Diagnosis of LI: Lactose malabsorption as positive glucose test, max rise <1.3mmol/l Diet: Self reported Diet assessment: NS Control for bias: None	Test: Blood glucose test Race: NS Ethnicity: NS
Birge, 1967[2] Country: USA Population: Adults 50 years or over Source: Patients referred to the National Institute of Arthritis and Metabolic Diseases Study design: Cross-sectional	Inclusion: Confirmed diagnosis of osteoporosis, healthy volunteers without osteoporosis Exclusion: History of steroid therapy, malabsopriton, endocrinopathy, cancer, renal disease or lithiasis or other causes of demineralization Excluded: NR Inclusion age: >50 Followup: None Mean age: NS	Diagnosis of LI: Positive lactose tolerance test; Patients who had less than a 50% mg/dl rise in blood glucose were lactase deficient Diet: Self reported Diet assessment: Interviews conducted by a registered dietician and PI Control for bias: None	Test: Oral lactose tolerance tests, glucose tolerance test, jejunal biopsy with impaired lactase activity Race: NS Ethnicity: NS
Buchowski, 2002[3] Country: USA Population: Premenopausal lactose maldigesting African American women Source: Recruited in Meharry Medical College Study design: Cross-sectional	Inclusion: Premenopausal (self-reported frequency of menstruation in the preceding three-month period)African American women with a rise in breath hydrogen concentration of greater than 0.90 mol/L (20 ppm) after ingestion of 25 g of lactose Exclusion: NR Excluded: Seven women were excluded from final analyses; two withdrew from the study, and five women did not complete dietary records Inclusion age: Adults Followup: None Mean age: 34.1-37.1	Diagnosis of LI: Lactose maldigestion – positive hydrogen breath testing. Lactose intolerance self reported symptoms were scored, women with scores of at least 3 on this scale after ingesting lactose-containing milk were classified as lactose intolerant. Women who scored 2 or less after drinking lactose containing milk were classified as lactose tolerant Diet: Regular diet Diet assessment: Seven-day dietary record Control for bias: Matching by age, adjustment for BMI	Test: The occurrence and severity of symptoms were self-rated by the subjects after ingesting 250 mL of lactose containing or lactose-free milk (Suarez et al.) Subjects reported occurrence and severity of abdominal fullness or cramps, flatulence, and diarrhea on a 0-5 scale as follows: 0 no symptoms, 1 trivial, 2 mild, 3 moderate, 4 strong, and 5 severe. Race: African-American Ethnicity: NR
Corazza, 1995[4] Country: Italy Population: Postmenopausal women Source: Clinic based Study design: Cross-sectional	Inclusion: 83 consecutive postmenopausal women with suspected osteoporosis, Caucasian, residents in the Bologna area Exclusion: Ovariectomy , estrogen replacement therapy, Ca supplementation,	Diagnosis of LI: Self reported relationship between the onset of abdominal symptoms, such as flatulence, abdominal pain, diarrhea and the intake of milk, ice cream, cheese and yoghurt and positive Hydrogen breath testing	Test: Positive hydrogen breath test Race: Caucasian Ethnicity: Caucasian

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	gastrointestinal diseases, recent treatment with antibiotics or drugs which could modify the intestinal flora, diseases known to influence Ca and bone metabolism Excluded: 25 Inclusion age: Adults Followup: NA Mean age: 57±7	Diet: Self reported Diet assessment: Dietary diary for three consecutive days evaluated by the nutritionist blinded to the details of the study Control for bias: None	
Di Stefano, 2002[5] Country: Italy Population: Adults Source: Work place Study design: Cross-sectional	Inclusion: 103 healthy subjects (59 women, 44 men), members of medical or paramedical staff of our hospital, or were students Exclusion: NR Excluded: NR Inclusion age: Adults Followup: NA Mean age: 28± 2	Diagnosis of LI: Lactose malabsorption was defined as positive hydrogen breath test Diet: Self reported Diet assessment: Dietary diary for 3 nonconsecutive days evaluated by blinded to the study details researcher Control for bias: None	Test: Self reported symptoms during the test and the 24-hour period after the test. Bloating, abdominal pain or cramps, diarrhea, and flatulence were ranked as follows: 0absence of symptoms, 1 trivial symptoms, 2 mild symptoms, 3 moderate symptoms, 4 strong symptoms, and 5 severe symptoms Race: Caucasian Ethnicity: NS
Du, 2002[6] Country: China Population: Adolescent Girls Source: Population based Study design: Cross-sectional	Inclusion: A random sample of 649 girls, ages 12–14 years from a sample of 1,277 girls selected in 13 middle schools in the Beijing area using cluster sampling procedure by means of a socioeconomic strata Exclusion: Evidence of liver, kidney, or other disorders that may have caused abnormal bone metabolism Excluded: NR Inclusion age: 12–14 years Followup: NA Mean age: 12.9±0.6	Diagnosis of LI: Feeling uncomfortable after drinking milk including symptoms such as stomach upset, cramps, bloating, and diarrhea, or any minor abnormal feeling Diet: Self reported Diet assessment: Habitual food and nutrient intakes over the past year were estimated by use of a specially designed and validated semi quantitative food frequency questionnaire Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: Asian
Enattah, 2004[7] Country: Finland Population: Young men Source: Population based cohort The Cardiovascular Risk in Young Finns Study Study design: Cross-sectional	Inclusion: Participants in a study examining the role of genes, hormones, and lifestyle factors: 234 young men, ages 18.3 to 20.6 years, 184 men were recruits of the Finnish Army, and 50 were men of similar age who had postponed their military service for reasons not related to health Exclusion: Not reported Excluded: NR Inclusion age: 18.3-20.6	Diagnosis of LI: Adult-type hypolactasia, caused by the lactase-phlorizin hydrolase C/C-13910 genotype Diet: Self reported Diet assessment: Calcium intake was calculated on the basis of the supply from dairy products only Control for bias: Adjustment	Test: lactase-phlorizin hydrolase C/T-13910 polymorphism Race: Caucasian Ethnicity: NS

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	Followup: NA Mean age: 19.4-19.7		
Enattah, 2005[8] Country: Finland Population: Postmenopausal women Source: Population based cohort The Cardiovascular Risk in Young Finns Study Study design: Cross-sectional	Inclusion: A random subset of the control group participating in an ongoing RCT of an educational program for the prevention of fractures. RCT study population was 2,181 postmenopausal women, ages 60–70 years living in Southern Finland, they were initially recruited from the population register between 1996 and 2000;.52 women 69–85 years old, participants in trials of drug treatment of osteoporosis, were included for genotyping if they had vertebral fracture or osteoporosis according to the WHO criteria of BMD (a T-score <-2.5) at either the lumbar spine or the femoral neck Exclusion: Metabolic bone disease other than postmenopausal osteoporosis, use of bone-active agents (any previous use of bisphosphonates, concomitant use of oral glucocorticoids, or hormone replacement therapy use less than 6 months before the study), diseases that affect bone turnover, history of gastrointestinal mucosal disorders (erosive gastritis, gastric ulcer or esophagitis), history of a prior thromboembolic disease, liver or kidney disease, insulin-treated diabetes, history of uterus or breast cancer, or uncontrolled hypertension. Control group was 59 healthy women of the same age Excluded: 2 women who did not answer the question about self perceived LI Inclusion age: >60 Followup: NA Mean age: 62-78	Diagnosis of LI: Adult-type hypolactasia, caused by the lactase-phlorizin hydrolase C/C-13910 genotype Diet: Self reported Diet assessment: Calcium intake was calculated from dairy products only. The questionnaire was not validated. Control for bias: Adjustment	Test: lactase-phlorizin hydrolase C/T-13910 polymorphism and self reported LI Race: Caucasian Ethnicity: NS
Enattah, 2005[9] Country: Finland Population: Elderly Source: Population based cohort The Cardiovascular Risk in Young Finns Study Study design: Prospective	Inclusion: Vantaa 85+ population-based study of all subjects born before April 1, 1906, who were living in the city of Vantaa, Finland, on April 1, 1991; included 483 people older than 85 years of age (106 men and 377 women). Exclusion: NR	Diagnosis of LI: Adult-type hypolactasia, caused by the lactase-phlorizin hydrolase C/C-13910 genotype Diet: Self reported Diet assessment: The data on consumption of milk was based on interviews of the participants	Test: lactase-phlorizin hydrolase C/T-13910 polymorphism Race: Caucasian Ethnicity: NS

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
cohort	Excluded: The data on milk product intake was available on 399 of 483 subjects Inclusion age: 85 - 98 Followup: 8 years Mean age: 89	Control for bias: Adjustment	
Finkenstedt, 1986[10] Country: Austria Population: Women Source: NS Study design: Case-control	Inclusion: Cases- women with "idiopathic" osteoporosis confirmed by the presence of reduced bone mineral density in plain x-ray films and either a femoral trabecular index <5 in 4 degree or the presence of spontaneous fractures of vertebrae or long bones, or both. Controls: 33 women without osteoporosis (Singh index >4) of the same ethnic origin matched for age Exclusion: Endocrine disorders, liver and renal disease, postgastrectomy states, malabsorption syndromes, rheumatoid arthritis, osteomalacia, and malignancy and patients receiving corticosteroids. Patients and controls were not taking drugs that influenced calcium or bone metabolism Excluded: NR Inclusion age: Adults Followup: NA Mean age: 54-56	Diagnosis of LI: Lactose malabsorption as a rise in glucose concentration of <20 mg/100 ml) after the ingestion of 50 g lactose dissolved in water Diet: Self reported Diet assessment: A questionnaire about mean daily or weekly ingestion of dairy products and about tolerance to milk in childhood and later life. The daily calcium intake derived from milk and dairy products was calculated according to standard nutritional tables Control for bias: Matching	Test: Self reported symptoms related to milk intolerance and diagnosis of lactose intolerance Race: Caucasian Ethnicity: Caucasian
Goulding, 1999[11] Country: New Zealand Population: Middle age and older women Source: Population based Study design: Prospective	Inclusion: Healthy Caucasian women ages 40-79 years Exclusion: Medications affecting bones, history of gastro-intestinal surgery, radiotherapy, hip replacement, malapsorption syndromes, hyperthyroidism, hyperparathyroidism Excluded: NR Inclusion age: 40-79 Followup: 1 year Mean age: NR	Diagnosis of LI: Lactose malabsorption: Positive hydrogen test, >10ppmH2 above baseline 60-180min after lactose load Diet: Self reported Diet assessment: Food frequency questionnaire and 4-day diet records Control for bias: Adjustment	Test: breath hydrogen after a 50 g oral lactose tolerance test Race: Caucasian Ethnicity: NR
Gugatschka, 2005[12] Country: Austria Population: Adult males Source: Population based and out-patient in the Division of Endocrinology and Nuclear	Inclusion: Participants in the population-based study by the Austrian Study Group on Normative Values on Bone Metabolism and out-patients who had examination of bone metabolism and nutritional and constitutional factors, response rate 56%	Diagnosis of LI: Lactose malabsorption was diagnosed when the difference between breath hydrogen concentration at baseline and maximum exceeded 20 parts per million according to international standards (ppm).	Test: Self reported symptoms related to milk intolerance and diagnosis of lactose intolerance Race: Caucasian Ethnicity: Caucasian

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Medicine Study design: Cross-sectional	Exclusion: Liver or kidney disease, primary hyperparathyroidism, long-term use of corticosteroids, other possible causes of secondary osteoporosis, consumption of bone-active medication, alcoholism Excluded: Breath hydrogen test was performed in 52 women (22%) Inclusion age: Adults Followup: NA Mean age: 56±12	Diet: Self reported Diet assessment: Calcium intake from dairy and other food products and self perceived lactose intolerance (nonmilk drinkers) were obtained using a questionnaire Control for bias: None	
Gugatschka, 2007[13] Country: Austria Population: Elderly male Source: Population based and out-patient in the Division of Endocrinology and Nuclear Medicine Study design: Cross-sectional	Inclusion: Participants in the population-based study by the Austrian Study Group on Normative Values on Bone Metabolism and out-patients who had examination of bone metabolism and nutritional and constitutional factors, response rate 56% Exclusion: Liver or kidney disease, primary hyperparathyroidism, long-term use of corticosteroids, other possible causes of secondary osteoporosis, consumption of bone-active medication, alcoholism Excluded: Breath hydrogen test was performed in 52 women (22%) Inclusion age: Elderly Followup: NA Mean age: 61±9	Diagnosis of LI: Lactose malabsorption was diagnosed when the difference between breath hydrogen concentration at baseline and maximum exceeded 20 parts per million according to international standards (ppm). Diet: Self reported Diet assessment: Standardized calcium questionnaire Control for bias: None	Test: Self reported symptoms related to milk intolerance and diagnosis of lactose intolerance Race: Caucasian Ethnicity: Caucasian
Harma, 1988[14] Country: Finland Population: Elderly women Source: Hospital based Study design: Case-control	Inclusion: Cases: 18 women with spinal fragility fractures and 28 women with hip fractures within one week after the fracture. Healthy controls: 35 female of the same ethnic background hospitalized for cataract surgery or other minor operations Exclusion: Institutionalized patients, previous gastric surgery, hepatic or renal failure, metabolic bone diseases, drugs altering bone metabolism Excluded: NR Inclusion age: 38-84 with spinal fractures, 64-93 with hip fractures, and 45-86 healthy controls) Followup: NA Mean age: 67-78 years	Diagnosis of LI: Lactose malabsorpion as positive blood glucose test (<1.3mmol/L) Diet: Self reported Diet assessment: Interview to assess daily milk consumption Control for bias: Matching	Test: Blood glucose test Race: Caucasian Ethnicity: Caucasian
Honkanen, 1997[15]	Inclusion: A random population sample of	Diagnosis of LI: Positive lactose tolerance	Test: Lactose tolerance test and

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Country: Finland Population: Perimenopausal women Source: Population based Study design: Cross-sectional	11,619 women of the 13,100 respondents who also responded to the fracture and health disorder questions. A random stratified sample of 3,222 of these 13,100 women underwent bone densitometry. Exclusion: Not reported Excluded: NR Inclusion age: NR Followup: None Mean age: 52.4± 2.9	test Diet: Self reported Diet assessment: Dairy calcium intake was computed as the sum intake from fluid milk products (l20 mg/dL) and cheese (87 mg/ slice) in 1989. The validity of the dairy calcium intake inquiry was tested against a 4 day food record of total nutritional calcium intake 76 women, resulting in a correlation of 0.50 Control for bias: Adjustment	abdominal symptoms during the test Race: Caucasian Ethnicity: NS
Honkanen, 1996[16] Country: Finland Population: Perimenopausal women Source: Population based Study design: Cross-sectional	Inclusion: A random population sample of 2,025 women 48-59 years old, who underwent spinal and femoral BMD measurement with dual x-ray absorptiometry in Kuopio, Finland, during 1989-1991 Exclusion: Not reported Excluded: NS Inclusion age: 47-56 Followup: None Mean age: 54±9	Diagnosis of LI: Positive lactose tolerance test (serial blood glucose determinations after a 50 g oral dose of lactose). Diet: Self reported Diet assessment: Dairy calcium intake was estimated with two questions: (1) “How many deciliters of milk products (such as milk, buttermilk, processed sour milk, and yogurt) do you use daily on average?” and (2) “How many slices of cheese do you use daily on average?” Dairy calcium intake was computed as the sum of calcium derived from fluid milk products (120 mg/dL) and cheese (87 mglslice) based on the NUTRICA, a PC-program for nutritional data developed by the Social Insurance Institution of Finland. The validity of the questionnaire was tested against a 4-day food record completed by 76 women (39 LI and 37 control women) in 1990. Control for bias: Adjustment	Test: Lactose tolerance test and abdominal symptoms during the test Race: Caucasian Ethnicity: NS
Horowitz, 1987[17] Country: Austria Population: Postmenopausal women Source: Clinic based Study design: Cross-sectional	Inclusion: 48 randomly selected untreated women with postmenopausal osteoporosis from 50 to 83 years Exclusion: Recent fractures Excluded: NR Inclusion age: 50-83 Followup: NA Mean age: 65	Diagnosis of LI: Lactose malabsorpion as positive hydrogen breath test, LI- self reported symptoms during and after the test Diet: Self reported Diet assessment: Questionnaire to record milk intake before the diagnosis of osteo-porosis and the presence of symptoms of LI Control for bias: None	Test: Breath hydrogen and interview by blinded to the results of the test researchers to assess symptoms of LI Race: NR Ethnicity: NR
Infante, 2000[18] Country: Spain Population: Children and	Inclusion: Thirty children followed dietary advice to exclude dairy for at least 2 years: 10 patients with late-onset, genetically	Diagnosis of LI: Medical diagnosis Diet: Advised Diet assessment: Questionnaire	Test: NS Race: NS Ethnicity: NS

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
adolescents Source: Clinic based Study design: Cross-sectional	induced lactose intolerance (breath hydrogen test >20 ppm), 3 patients with short bowel syndrome, 7 with cow's milk protein allergy and l0 with hypercholesterolemia (cholesterol >200 mg/dl and low-density lipoprotein cholesterol >130 mg/ dl).14 patients received special formulas for children (lactose-free cow's milk formula, highly hydrolyzed cow's milk protein formula, soy protein isolate formula), 4 patients received liquid soy beverages, 6 patients received skim milk (1% fat), and 6 patients had exclusion of dairy products. Exclusion: NR Excluded: NR Inclusion age: 2-14 years Followup: NA Mean age: 7	commenting dairy food (or substitute)o consumption for a total of 7 days during a 4-week period Control for bias: None	
Kanis, 2005[19] Country: UK Population: Adults Source: Population based Study design: Meta-analysis of individual patient data	Inclusion: Meta-analysis of the original data from 6 prospective cohorts that recruited randomly selected from the populations in Europe, Australia, and Canada 39,563 men and women. The collaborative study to identify clinical risk factors for fracture included the European Vertebral Osteoporosis Study (EVOS/EPOS study), the Canadian Multicentre Osteoporosis Study (CaMos), the Dubbo Osteoporosis Epidemiology Study (DOES), the Rotterdam Study, the Sheffield Study and a cohort from Gothenburg. Exclusion: Invalidated data on milk consumption Excluded: NR Inclusion age: Adults Followup: Total 3.8 years, 151,957 person years for 39,563 subjects Mean age: Varied in the studies, the ranges 21-103	Diagnosis of LI: Reference category of low milk intake <1 glass of milk/day (~250 mg calcium/ day). A threshold of <500 mg of calcium was used two studies (Rotterdam and DOES) assuming that ~50% of calcium intake is in the form of milk. Diet: Self reported Diet assessment: Validated food frequency questionnaire or dietary intake questionnaire Control for bias: Adjustment	Test: Not addressed Race: NS Ethnicity: NS

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Kudlacek, 2002[20] Country: Austria Population: Adults Source: Clinical based screening Study design: Cross-sectional	Inclusion: Healthy individuals who were referred for confirmation of suspected osteoporosis or for osteoporosis screening and estimation of risk for fracture; male female ratio, 1:4 Exclusion: Secondary osteoporosis, medical treatment, e.g., receiving hormone replacement therapy, fluorides, calcitonin, or vitamin D, other gastrointestinal diseases, e.g., celiac disease or chronic inflammatory bowel disease, a history of fracture due to severe trauma. Excluded: NR Inclusion age: NR Followup: NA Mean age: 58.2± 11.5	Diagnosis of LI: Lactose intolerance was diagnosed with a positive hydrogen breath test. Lactose malabsorbers moderate, 20ppm <DH2 < 59ppm or was severe (DH2 >60ppm). Clinical symptoms were categorized as moderate (group 1) or severe (group 2). Symptoms during the test were scored with a self-reported questionnaire. Group 0 reported no symptoms; group 1 experienced abdominal discomfort (moderate symptoms); and group 2, severe diarrhea with abdominal cramps (severe symptoms). Diet: Self reported Diet assessment: Questionnaire to categorize as lactose exclusion (denied milk consumption), low lactose diet (1 glass per day ~ 200ml milk; 240mg calcium/day) no restrictions with regard to milk (>400ml milk; 480mg calcium/day). Control for bias: None	Test: Hydrogen breath test, self reported symptoms Race: Caucasian Ethnicity: Caucasian
Kull, 2009[21] Country: Estonia Population: Adults Source: Health care based: registers of general practitioners in the region Study design: Cross-sectional	Inclusion: Randomly selected from the registers healthy subjects, response rate 66% (200 F, 167 M) Exclusion: NR Inclusion age: >20 Followup: NA Mean age: 25-70	Diagnosis of LI: Adult-type hypolactasia was diagnosed by direct sequencing of the LCT gene Diet: Self reported Diet assessment: Questionnaire about milk and dairy product consumption, self-perceived milk tolerance Control for bias: None	Test: Self-reported milk intolerance and direct sequencing of the LCT gene Race: Caucasian Ethnicity: Caucasian
Lehtimaki, 2006[22] Country: Finland Population: children and adolescents Source: Population based cohort The Cardiovascular Risk in Young Finns Study Study design: Prospective cohort	Inclusion: A random sample from the national population register, from 5 university cities in Finland and the rural municipalities in their vicinity Exclusion: Not reported Excluded: 2,265 from original 3,596 participants had genotyping exam Inclusion age: 3-18 years Followup: 21 years Mean age: 10	Diagnosis of LI: Adult-type hypolactasia, caused by the lactase-phlorizin hydrolase C/C-13910 genotype Diet: Self reported Diet assessment: Dietary questionnaires, detailed dietary interviews, and a 48-hour dietary recall Control for bias: Stratification by sex and onset of LI	Test: Lactase-phlorizin hydrolase C/T-13910 polymorphism Race: Caucasian Ethnicity: NS
Matlik, 2007[23] Country: USA Population: 10-13 year old female adolescents	Inclusion: Middle schools that had larger proportions of Asian or Hispanic students than the state average and were located within a 1-hour distance from the designated	Diagnosis of LI: Lactose maldigestion diagnosed with hydrogen breath testing (breath hydrogen levels of >20 ppm), perceived milk intolerance diagnosed with	Test: Perceived milk intolerance was diagnosed with questionnaire included 3 statements derived from focus

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Source: Participants in a sub study of the multiple-site project Adequate Calcium Today Study design: Cross-sectional study was a sub study of the Adequate Calcium Today (ACT) project, a school-randomized intervention project conducted at sites in 6 states	dual-energy x-ray absorptiometry (DXA) measurement site (1 site in each state).Girls were eligible if they were at least 75% Asian, Hispanic, or non-Hispanic white, as self-reported by their biological parents Exclusion: Estimated daily food calcium intakes that were 100 mg/day or 2,500 mg/day were considered improbable, and individuals with such values were excluded from any analyses using food calcium intake. Excluded: A total of 39 (13.5%) of 289 subjects were excluded Inclusion age: 10-13 years Followup: None Mean age: 11.	questionnaires Diet: Self reported diet Diet assessment: Calcium-specific, semi quantitative, food frequency questionnaire developed for and evaluated with Asian, Hispanic, and non-Hispanic white youths Control for bias: Adjustment	group discussions with a sample of adolescents representing the same age group and race/ethnic groups as the ACT participants.30 The statements were as follows: (1) “I am allergic to milk,” (2) “I get a stomachache after drinking milk,” and (3) “I have been told that milk will make my stomach hurt after I drink it.” Responses were “strongly disagree” (scored as 1) to “strongly agree” (scored as 5) or “do not know” (scored as missing). A PMI score was calculated as a mean of the responses. The frequency of responses separated distinctly above 2; therefore, a score of 2 was defined to be indicative of PMI Race: Among 230 girls :65 Asian, 76 Hispanic, and 89 non-Hispanic white
Obermayer-Pietsch, 2007[24] Country: Austria Population: Postmenopausal women Source: Participants in a genetic screening study for osteoporosis Study design: Prospective followup of the previously published study	Inclusion: Unrelated postmenopausal women who live independently Exclusion: Liver or kidney disease, primary hyperparathyroidism or other causes of bone disease Excluded: 60 Inclusion age: Adults Followup: 61±9months Mean age: 65±9	Diagnosis of LI: Hydrogen breath test and glucose blood test, symptoms Diet: Self reported Diet assessment: Detailed food-frequency questionnaire on dietary calcium intake in milligrams per day Control for bias: None	Test: LCT genotypes TT, TC, and CC Race: NR Ethnicity: NR
Obermayer-Pietsch, 2004[25] Country: Austria Population: Postmenopausal women Source: Participants in a genetic screening study for osteoporosis Study design: Cross-sectional study	Inclusion: Unrelated postmenopausal women Exclusion: Liver or kidney disease, primary hyperparathyroidism, other causes of secondary bone disease, consumption of bone active medication Excluded: 92 Inclusion age: Adults Followup: None Mean age: 62 ± 9	Diagnosis of LI: Recorded by the general practitioner during the standardized interview, self reported dislike of milk taste, and aversion to milk consumption Diet: Self reported Diet assessment: Detailed food-frequency questionnaire on dietary calcium intake in milligrams per day Control for bias: Adjustment	Test: LCT genotypes TT, TC, and CC Race: NR Ethnicity: NR

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Segal, 2003[26] Country: Israel Population: Adults Source: Clinic based Study design: Cross-sectional	Inclusion: Seventy-eight consecutive patients 20 to 78 years of age, with clinical signs of LI referred to gastroenterologists or recruited from the Gastroenterology Unit Exclusion: Ontogenesiimperfect; chronic renal failure; hypocalciuric hypercalcemia; history of recent malignancy Excluded: 12 Inclusion age: 20-78 Followup: NA Mean age: 66 patients, 49 women (18 premenopausal, 31 postmenopausal), 17 men	Diagnosis of LI: Positive breath test in addition to clinical symptoms (concentration of H2 in the expired air increased by more than 20 ppm above baseline) Diet: Self reported Diet assessment: Calcium intake from dairy and other sources was evaluated using a semi-quantitative food frequency questionnaire adapted from W. Willet Control for bias: Matching by age and gender	Test: Clinical diagnosis was confirmed in all patients by positive breath test. Race: NS Ethnicity: NS
Stallings, 1994[27] Country: USA Population: Prepubertal children Source: Children's Hospital of Philadelphia Study design: Cross sectional controlled comparison	Inclusion: Prepubertal children 6-12 years with LI diagnosed with standard breath hydrogen test within the previous 3 years, without symptoms related to LI at the time of the study. Healthy children participating in the Fels Longitudinal Study Exclusion: Significant illnesses that could affect growth or bone development including inflammatory bowel syndrome, renal failure, cardiac disease, sarcoidosis. Consume Ca++ supplement and/or>16oz milk products Excluded: One girl without suitable control Inclusion age: 6-12 years Followup: None Mean age: 9.6±1.9	Diagnosis of LI: LI diagnosed by standard breath hydrogen test Diet: prescribed low lactose diet Diet assessment: Food frequency questionnaire of 7 days over 6 week period to evaluate adherence to prescribed diet Control for bias: Matching, Adjustment for body size	Test: Breath hydrogen test Race: NR Ethnicity: NR.
Vigorita, 1987[28] Country: USA Population: Postmenopausal women Source: NS Study design: Cross-sectional	Inclusion: Postmenopausal women with the osteoporotic spinal compression fracture syndrome Exclusion: Concurrent malabsorption syndromes, endocrinopathies, marrow tumor, or prior therapy Excluded: 3 women with normal and 6 women with abnormal lactose tolerance test were excluded from bone biopsy analyses Inclusion age: >53 Followup: None Mean age: 66.3-70.3	Diagnosis of LI: Positive lactose tolerance test; Patients who had less than a 30% mg/dl rise in blood glucose were termed lactase deficient Diet: Self reported Diet assessment: Interviews conducted by a registered dietician using a questionnaire based on dietary preference, 24-hour recall, and weekly intake Control for bias: None	Test: Oral lactose tolerance tests Race: Caucasian Ethnicity: All Whites, not Hispanic
Wheadon, 1991[29] Country: New Zealand Population: Elderly New	Inclusion: Cases-women <75 years of age with hip fractures 6 months-2 years before the study diagnosed with type II	Diagnosis of LI: Lactose malabsorption-breath hydrogen after a 50 g oral lactose tolerance test of >10ppm above baseline	Test: breath hydrogen after a 50 g oral lactose tolerance test Race: Caucasian

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Zealand women with hip fractures Source: NS Study design: Case-control	osteoporosis. Controls: 16 healthy age-matched women who had never had a fracture and 50 healthy young volunteers (17-30 years old) Exclusion: Previous surgery of gastro-intestinal tract, baseline reasons for malabsorption Excluded: NR Inclusion age: Cases-<75 years old, age matched controls, healthy controls 17-30 years Followup: NA Mean age: 66±10	Diet: Self reported Diet assessment: Dietary calcium was estimated from a food frequency questionnaire Control for bias: Age matched controls	Ethnicity: 1 women from India
Studies of low lactose diet that did not address lactose intolerance status			
Appleby, 2007[30] Country: UK Population: Vegetarians; adults Source: The Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) Study design: Prospective cohort	Inclusion: The Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) general practice surgeries recruited 57,450 adults from the residential areas and several general practice surgeries in the UK Exclusion: NR Excluded: 240 participants who did not answer the question about fractures, 1,360 who reported any type of fracture before recruitment or a fracture of the digits or ribs, and 660 whose nutrient intake data were considered to be unreliable (>20% of food frequencies missing or daily energy intakes less than 800 kcal or more than 4,000 kcal for men or less than 500 kcal or more than 3,500 kcal for women). Inclusion age: NR Followup: 6 years Mean age: 46.6	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Food frequency questionnaire Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR
Bauer, 1993[31] Country: USA Population: Older women Source: The Study of Osteoporotic Fractures Research Group Study design: Cross-sectional	Inclusion: 9,704 ambulatory, nonblack women, ages 65 years or older Exclusion: Blacks or unable to walk without the assistance of another person or who had bilateral hip replacements Excluded: NR Inclusion age: >65 Followup: NA Mean age: 71.1	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Checklist-interview method developed from the HANES-II survey to asses dietary Ca++ (correlation of 0.76 with calcium intake assessed by a 7-day diet diary) and milk intake Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: Whites Calcium intake from milk as a teenager, between ages 18 and 50, and after age 50 years, adjusted for current calcium intake, was associated with increased bone mass: women

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
			who drank milk at every meal, between ages 18 and 50, had 3.1% higher bone mass compared with those who rarely or never drank milk
Black, 2002[32] Country: New Zealand Population: Prepubertal children with a history of long-term milk avoidance Source: Population based Study design: Cross-sectional	Inclusion: Caucasian children ages 3–10 years with a history of prolonged milk avoidance for more than 4 months Exclusion: Gait disorders, current bone fractures, or medical diagnoses affecting bone (e.g., diabetes or malabsorptive syndromes) Excluded: None Inclusion age: Children Followup: NA Mean age: 5.9±1.9 (female) and 6.4±2.3 (male)	Diagnosis of LI: Not diagnosed Diet: Self reported prolonged milk avoidance Diet assessment: Validated food-frequency questionnaire; current calcium intakes were estimated both by the same FFQ used at baseline and by 4-day diet records (4DDRs), which we collected just before the followup clinic appointment to avoid post interview bias. Control for bias: None	Test: Self reported symptoms related to milk avoidance Race: Caucasian Ethnicity: NR Sex-specific, age-adjusted Z scores were derived from a reference population of 100 boys and 100 girls without history of fracture or milk avoidance living in Dunedin
Chiu, 1997[33] Country: Taiwan Population: Postmenopausal Taiwanese women Source: 10 temples in Tai-nan and Kaoshiung, two of the largest counties in southern Taiwan. Study design: Cross-sectional	Inclusion: 258 postmenopausal Buddhist nuns and female religious followers of Buddhism in southern Taiwan Exclusion: Disease or therapy known to affect bone metabolism Excluded: NR Inclusion age: 40–87 Followup: NA Mean age: 60.8 ± 9.2	Diagnosis of LI: Not addressed Diet: Vegan diet Diet assessment: Questionnaire interview to identify type of vegetarian practiced (strict vegan, lacto vegetarian, or omnivore who ate vegan diet only periodically). Long-term vegan vegetarians were defined in this study as those who had adhered to a strict vegan vegetarian diet for at least 15 years. Dietary assessment included a 24-hour recall and food frequency questionnaire Control for bias: Adjustment	Test: Not addressed Race: Asian Ethnicity: Asian
Cumming, 1994[34] Country: Australia Population: Elderly women and men Source: Population-based control Study design: Case-control	Inclusion: Cases-patients with acute hip fracture older than 65 years of age were recruited in 12 hospitals. Controls were selected in a defined region in Sydney, Australia, using an area probability sampling method, with additional sampling from nursing homes Exclusion: NR Excluded: Exposure data was not available for 42% of cases because of impaired cognitive function and difficulties collecting proxy responses Inclusion age: >75	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Interview administered questionnaire, proxy responders. To assess recall bias, all participants were asked what cases hip fractures in old age. Dairy intake was categorized in units, 1 unit of dairy products was equal 1 glass of milk+0.5 servings of chees+0.5 (milk on cereal) Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	Followup: NA Mean age: NR		
Feskanich, 1997[35] Country: USA Population: Middle aged women Source: The Nurses' Health Study Study design: Prospective cohort	Inclusion: 77,761 women, ages 34-59 years in 1980, who had never used calcium supplements were selected from the original cohort of 121,701 female registered nurses in 11 states who were 30 to 55 years of age when they returned an initial questionnaire in 1976 Exclusion: Implausibly low or high daily food intake or failure to report frequency of milk consumption (6%); a previous hip or forearm fracture or a diagnosis of coronary heart disease, stroke, cancer, or osteoporosis (6%); and reported use of calcium supplements in 1982 (9%). Excluded: 0.21 Inclusion age: 34-59 Followup: 12 years Mean age: 45.8-46.4	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Food-frequency questionnaire to collect four dairy items were added: cream or whipped cream, sour cream, sherbet or ice milk, and cream cheese. In validation studies the questionnaire was compared with multiple weeks of diet records, correlations were 0.81 for skim or low-fat milk, 0.62 for whole milk, and 0.57 for dietary calcium. In a reproducibility study that compared the frequency of milk consumption during their teenage years (ages 13 to 18) with data from a second administration 8 years later, the correlation was 0.71. Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: 98% of the cohort is White
Fujiwara, 1997[36] Country: Japan Population: Adults Source: The Adult Health Study Study design: Prospective cohort	Inclusion: 4,869 residents in Hiroshima and Nagasaki ages 32 years who responded to the mail questionnaire survey conducted in 1979–1981. Exclusion: Incident hip fractures due to traffic accidents Excluded: 285 who lacked measurements of height and weight and 11 who were diagnosed as having hip fracture in the 1978–1980 examination were excluded Inclusion age: >32 Followup: 18 Mean age: 58.5 ± 12.2	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Questionnaire survey about food frequency Control for bias: Adjustment	Test: Not addressed Race: Asian Ethnicity: Asian
Goulding, 2004[37] Country: New Zealand Population: Prepubertal children with a history of long-term milk avoidance Source: Population based Study design: Prospective followup of the previously published study	Inclusion: Caucasian children ages 3–10 years with a history of prolonged milk avoidance for more than 4 months Exclusion: Gait disorders, current bone fractures, or medical diagnoses affecting bone (e.g., diabetes or malabsorptive syndromes) Excluded: 4 Inclusion age: Children Followup: 2 years	Diagnosis of LI: Not diagnosed Diet: Self reported prolonged milk avoidance Diet assessment: Validated food-frequency questionnaire; current calcium intakes were estimated both by the same FFQ used at baseline and by 4-day diet records (4DDRs), which we collected just before the followup clinic appointment to avoid post interview bias.	Test: Self reported symptoms related to milk avoidance Race: Caucasian Ethnicity: NR Data from the Dunedin Multidisciplinary Health and Development Study (a birth cohort >1,000 children born in 1972/1973) was used to provide comparative fracture incidence in

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	Mean age: 3-10 years	Control for bias: None	the general community
Johansson, 2004[38] Country: UK Population: Elderly women Source: population based Study design: Placebo arm in RCT, prospective	Inclusion: 2,113 women >75 years of age randomly selected from Sheffield, UK, and adjacent regions who were randomized to placebo group in RCT of Ca++ supplement. 35,000 were invited, 5,873 responded (response rate 17%) Exclusion: Bone active agents, known malabsorption states, lack of compliance because of a poor mental state or concurrent illnesses, serum creatinine >0.3 mM, leukopenia (white cell count, <2 109/liter), hyper- or hypocalcemia, and elevated transaminases (greater than twice the upper reference limit). Excluded: 683 women randomized to placebo group Inclusion age: >75 Followup: 6 years Mean age: NR	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Questionnaire to record milk intake Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR
Johnell, 1995[39] Country: Sweden Population: Women Source: The MEDOS Study. Mediterranean Osteoporosis Study Study design: Case-control	Inclusion: Cases: 2,086 women ages 50 years or more with hip fracture (interviewed within 14 days of fracture) in 14 centers from Portugal, Spain, France, Italy, Greece, and Turkey. Controls: 3,532 women ages 50 years or more selected from the neighborhood or population registers Exclusion: Poor mental health, concurrent illness Excluded: 80% of cases and 84% of controls were intervwied Inclusion age: >50 Followup: NA Mean age: 77.7-78.1	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Cases and controls were interviewed using a structured questionnaire on consumption of milk. Ca++ from milk in the recent past, young adulthood and childhood was assessed with 5 point scale (0-4: never, sometimes, 1-2 glasses/day, 3-4 glasses/day, >5 glasses/day) An overall score was calculated from three measurements with max 12 points. The median score was 6~ lifetime 1-2 glasses of milk/day or 240-480mg Ca++/day Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR
Kalkwarf, 2003[40] Country: USA Population: Adults Source: Population based Study design: Cross-sectional	Inclusion: The third National Health and Nutrition Examination Survey of 3,251 non-Hispanic, white women age ≥20 not institutionalized in 1988 and 1994 using a stratified, multistage probability design to select a nationally representative sample Exclusion: Unacceptable bone measurements	Diagnosis of LI: Not defined Diet: Self reported Diet assessment: Milk intake during childhood was examined during the household interview with the questionnaire targeted 5 distinct age periods: childhood (5–12 years), adolescence (13–17 years), young adulthood (18–35 years), middle	Test: Not addressed Race: Caucasian Ethnicity: Non-Hispanic, white Among women ages 20-49 years, bone mineral content was 5.6% lower in those who consumed <1 serving of milk/week (low intake) than in those who consumed >1

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	Excluded: Exclusion of fractures associated with severe trauma did not affect the results Inclusion age: Adults Followup: NA Mean age: 35±8	adulthood (36–65 years), and later adulthood (> 65 years). Subjects were asked to recall how often they consumed any type of milk, responses were collapsed into 4 categories: >1/day, 1/day, 1–6/week, and <1/week. Current milk intake was derived from the food-frequency questionnaire with the same categories as the historical milk intake information. Calcium intake was estimated from the 24-hour recall conducted during the MEC visit. The 24-hour recall was conducted with the use of an automated, interactive dietary data-collection system that was developed by the University of Minnesota Nutrition Coordinating Center. Food composition data were based on the US Department of Agriculture data files specific for that time period Control for bias: Adjustment	serving/day (high intake) during childhood (P < 0.01). Low milk intake during adolescence was associated with a 3% reduction in hip bone mineral content and bone mineral density (P <0.02). Among women ages ≥50 years, there was a nonlinear association between milk intake during childhood and adolescence and hip bone mineral content and bone mineral density (P < 0.04).
Kelsey, 1992[41] Country: USA Population: Older women Source: The Study of Osteoporotic Fractures Research Group Study design: Cross-sectional	Inclusion: 9,704 ambulatory, nonblack women, ages 65 years or older Exclusion: Blacks or unable to walk without the assistance of another person or who had bilateral hip replacements Excluded: NR Inclusion age: >65 Followup: NA Mean age: 71.1	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Checklist-interview method developed from the HANES-II survey to asses dietary Ca++ (correlation of 0.76 with calcium intake assessed by a 7-day diet diary) and milk intake Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: Whites
Lau, 1998[42] Country: Hong Kong Population: Elderly Chinese vegetarian women Source: Population based Study design: Cross-sectional	Inclusion: 76 vegetarian for over 30 years noninstitutionalized Buddhist women (ages 70±89 years). 250 Chinese omnivorous women, participants in a previous dietary survey, served as controls Exclusion: NR Excluded: NR Inclusion age: 70-89 Followup: NA Mean age: 79.1±5.2	Diagnosis of LI: Not addressed Diet: Vegan diet Diet assessment: The 24 hour recall method administered by a single trained interviewer. Control for bias: None	Test: Not addressed Race: Asian Ethnicity: Asian
Looker, 1993[43] Country: USA Population: Men and posmenopausal women	Inclusion: Nationally representative sample of the United States population: 4,342 white men and postmenopausal women ages 50-74 years at baseline (1971-1975) were	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: 24-hour recall and qualitative food frequency questionnaire to	Test: Not addressed Race: Caucasian Ethnicity: Whites

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Source: the NHANES I Epidemiologic Follow-Up Study cohort Study design: Prospective cohort	observed through 1987 for up to 16 years of followup Exclusion: African American Excluded: NR Inclusion age: >50 Followup: 16 years Mean age: NR	obtain weekly frequency of dairy food consumption. Daily calcium intake was categorized: 0-405, 406-654, 655-1,003 and >1,004 for men; 0-300, 301-501, 502-776, and ≥777 for all women; 0-292, 293-500, 501-755 and >756 for late menopausal women. Daily Ca++intake was also categorized by selected cutoff points: <400 rag/day versus >600, > 800 or >1,000 rag/day. The food frequency questionnaire assessed weekly frequency, of milk and cheese consumption in the previous 3 months. Ca++ intake index combined both measurement. Control for bias: Adjustment	
Nieves, 1992[44] Country: USA Population: Middle aged women Source: Clinic based Study design: Case-control	Inclusion: Cases: 161 white women admitted to one of 30 participating hospitals with radiologically confirmed diagnosis of a first hip fracture. Controls included 168 white women from general and orthopedic surgical services frequency-matched to cases by age group and hospital. The response rate was 61% in the case group and 56% in the controls; respondents were similar to nonrespondents with respect to age and city Exclusion: Previous hip fracture or hip replacement; cognitive impairment, death prior to interview, severe language and hearing impairments or medical instability Excluded: 143 potential cases and 44 potential controls with proxy responses Inclusion age: >45 Followup: NA Mean age: 50-103	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Standardized questionnaire to all cases and controls to assess frequency of consumption of milk, cheese and dark green leafy vegetables was used to estimate calcium intake during the teen years Control for bias: Matching by age and hospital, adjustment for BMI, education, smoking, HRT, chronic disease	Test: Not addressed Race: Caucasian Ethnicity: Whites
Parsons, 1997[45] Country: The Netherlands Population: Adolescents Source: Macrobiotic families connected with the Human Nutrition Department, Wageningen University Study design: Cross-sectional	Inclusion: 195 adolescents (103 girls, 92 boys) ages 9-15 years who followed a macrobiotic diet in childhood (43 girls, 50 boys) and 102 (60 girls, 42 boys) control subjects; response rates of the families 50% Exclusion: Poor health, taking medications that can affect bone health Excluded: 10 families failed to keep appointments	Diagnosis of LI: Not addressed Diet: Macrobiotic children reported following a macrobiotic diet from birth onward for a period of 6.2 6 2.9 (mean 6 SD) years, in most cases subsequently adopting a vegetarian-type diet Diet assessment: Previously validated food frequency questionnaire with added questions to asses non dairy sources of	Test: Not addressed Race: Caucasian Ethnicity: NR

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
	Inclusion age: >9 Followup: NA Mean age: 11.6-12.5	Ca++ Control for bias: Adjustment	
Rockell, 2005[46] Country: New Zealand Population: Prepubertal children with a history of long-term milk avoidance Source: Population based Study design: Prospective followup of the previously published study	Inclusion: Caucasian children ages 3–10 years with a history of prolonged milk avoidance for more than 4 months Exclusion: Gait disorders, current bone fractures, or medical diagnoses affecting bone (e.g., diabetes or malabsorptive syndromes) Excluded: 4 Inclusion age: Children Followup: 2 years Mean age: 8.1±2	Diagnosis of LI: Not diagnosed Diet: Self reported prolonged milk avoidance Diet assessment: Validated food-frequency questionnaire; current calcium intakes were estimated both by the same FFQ used at baseline and by 4-day diet records (4DDRs), which we collected just before the followup clinic appointment to avoid post interview bias. Control for bias: None	Test: Self reported symptoms related to milk avoidance Race: Caucasian Ethnicity: NR Sex-specific, age-adjusted Z scores were derived from a reference population of 100 boys and 100 girls without history of fracture or milk avoidance living in Dunedin
Shaw, 1993[47] Country: Taiwan Population: Adults Source: Population based Study design: Cross-sectional	Inclusion: 404 healthy volunteers (266 women and 138 men, ages 15 to 83 years) living in Lin-Kou Township Exclusion: History of hip fracture, spine disorders, adrenal gland disorders Excluded: NR Inclusion age: 15-83 Followup: NA Mean age: NR	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Interview with a trained technician, food frequency questionnaire of 16 calcium-rich items common for Taiwan Control for bias: None	Test: Not addressed Race: Asian Ethnicity: Asian
Soroko, 1994[48] Country: USA Population: Older women Source: community based cohort of older women in California Study design: Cross-sectional	Inclusion: 624 postmenopausal White women Exclusion: No data on milk consumption history and had bone mineral density measurements Excluded: 43 Inclusion age: >60 Followup: NA Mean age: 70.6	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Standardized interview with food-frequency questionnaire to assess current dietary calcium intake and calcium supplementation history. Participants also quantified their daily milk consumption during adolescence (12 to 19 years of age), midlife (20 to 50 years of age), and older adulthood (after 50 years of age) as (1) "rarely or never" (classified as none), (2) "about every week, but not every day" (low), (3) "1 to 2 glasses per day, about every day" (medium), or (4) "3 or more glasses per day, about every meal" (high). Childhood milk intake was not queried because of expected poor recall. Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: Whites Higher milk consumption in adulthood was independently and significantly associated with higher bone mineral density levels at the mid radius, spine, total hip, intertrochanter, and trochanter. Higher teenage milk intake was associated with significantly higher bone mineral density at the spine and mid radius. Milk intake was not associated with bone mineral density of the ultradistal wrist. Analyses stratified by calcium supplementation revealed similar patterns

Appendix Table D1. Observational studies of lactose intolerance or malabsorption in association with patient outcomes (continued)

Study	Subjects	Diagnosis and Control for Bias	Comments
Tavani, 1995[49] Country: Italy Population: Postmenopausal women Source: 4 largest teaching and general hospitals in Milan Study design: Case-control	Inclusion: Cases: 241 postmenopausal women (median age 64 years, range 45-74 years) admitted to hospital for fracture of the hip. Controls- 719 controls hospitalized patients for acute, non-neoplastic, nontraumatic, nondigestive, non-hormone-related diseases Exclusion: Long-term modifications in diet Excluded: NR Inclusion age: 45-74 Followup: NA Mean age: 64	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Trained interviewers used a structured questionnaire to collect data on frequency of 29 food items before the onset of the disease including major sources of calcium Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR
Turner, 1998[50] Country: USA Population: Older women Source: The Third National Health and Nutritional Examination Survey, Phase 1 Study design: Cross-sectional	Inclusion: National sample of 953 southern women ages 50 years and older Exclusion: NR Excluded: NR Inclusion age: >50 Followup: NA Mean age: 68.8 ±11.5	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Food-frequency questionnaire Control for bias: Adjustment	Test: Not addressed Race: 58% Caucasian, 27.6 African American, 14.7% Asian
Vatanparast, 2005[51] Country: Canada Population: children and adolescents Source: Population based Study design: Prospective cohort	Inclusion: Participants in the University of Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS)-population-based sample of children in Saskatoon.7-year longitudinal data from 85 boys and 67 girls are analyzed Exclusion: History of chronic disease or chronic medication use, medical conditions, allergies, or medication use known to influence bone metabolism or calcium balance Excluded: NR Inclusion age: 8-20 years Followup: 7 years Mean age: 11.8±0.9 for girls; 13.5±1 for boys	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Dietary intake was assessed by serial 24-hour recalls Control for bias: Adjustment	Test: Not addressed Race: Caucasian Ethnicity: Caucasian For every additional 1 mg calcium consumed by boys, 0.017 g BMC was accrued
Wyshak, 1989[52] Country: USA Population: Women Source: University based Study design: Cross-sectional	Inclusion: 5,398 alumnae listed as currently alive by the alumnae offices of 8 colleges and two universities, response rate 71% Exclusion: NR Excluded: NR Inclusion age: >21 Followup: NA Mean age: 51.3 ±0.2	Diagnosis of LI: Not addressed Diet: Self reported Diet assessment: Questionnaire to asses any dietary restrictions including low milk intake Control for bias: Adjustment	Test: Not addressed Race: NR Ethnicity: NR

NS - not specified, NA - not applicable, NR - not reported

Appendix Table D2. Association between low dairy Ca++ intake and bone fractures

Study	Comparison	Outcome	Estimate	Mean (95% CI)
Goulding, 2004[37] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Calcium intake below 300 mg/day vs. >300mg/day	History of fracture	Crude OR	1.26 (0.34; 4.65)
Looker, 1993[43] Country: USA Men and postmenopausal women Ca++ intake difference in comparison groups: NR/Y	Selected calcium cut points (mg~day) <400 vs. >1,000 in men	History of fracture	Adjusted for alcohol use, smoking, physical activity, BMI, and postmenopausal hormone use in the total sample of women in addition to age RR	0.51 (0.20; 1.10)
	Selected calcium cut points (mg~day) <400 vs. >1,000 in women			0.91 (0.50; 1.60)
	Selected calcium cut points (mg~day) <400 vs., >1,000 in late menopausal women			0.73 (0.30; 1.60)
Tavani, 1995[49] Country: Italy Postmenopausal women Ca++ intake difference in comparison groups: NR/NR	Ca++ intake >1,026mg/day vs. <443mg/day	Hip fracture	Adjusted for age, education, smoking status, total alcohol consumption, and estrogen replacement therapy OR	1.20 (0.80; 2.00)

Appendix Table D3. Association between lactose intake and genetic polymorphism or self reported lactose intolerance

Study	Comparison	Outcome	Results	
Lehtimaki, 2006[22] Country: Finland Children and adolescents	T/T vs. C/C	Lactose-free or low lactose diet	Statistically insignificant after adjustment for baseline dietary calcium intake, pubertal stage, age, and study area	
	C/T vs. C/C			
	T/T vs. C/T			
	T/T vs. C/C in women		products were significantly lower for subjects with the C/C-13910 genotype than the other genotypes over the study years 1980, 1986, and 2001.	
	C/T vs. C/C in women			
	T/T vs./ C/T in women			
	T/T vs. C/C in men		genotype differences in the intake of calcium over the study years, but the consumption of milk and milk products was significantly lower for subjects with the C/C-13910 genotype over the study years from 1980 to 2001 For male subjects >10 years of age, the consumption of milk and dairy products was significantly lower for subjects with the C/C-13910 genotype over the study years from 1980 to 2001.	
	C/T vs. C/C in men			
	T/T vs./ C/T in men			
			Estimate	**Mean (95%CI)**
Enattah, 2005[9] Country: Finland Elderly	T/T or T/C vs. C/C	Use of milk products	OR	**2.06 (1.38; 3.06)**
Country: Austria Adult males	T/T vs. C/C			**3.79 (1.02; 14.15)**
	C/T vs. C/C			1.84 (0.84; 4.03)
	T/T vs. C/T			2.07 (0.57; 7.44)
Kull, 2009[21] Country: Estonia Adults	T/T vs. C/C	Milk consumption (dL/day)	Mean Difference	**1.00 (0.34; 1.66)**
	C/T vs. C/C			**0.80 (0.21; 1.39)**
	T/T vs. C/T			0.20 (-0.51; 0.91)
	Hypolactasia vs. normolactasia			**-0.80 (-1.32; -0.28)**
	Self reported LI vs. none			**-1.40 (-2.12; -0.68)**

Appendix Table D4. Association between low lactose diets, lactose intolerance or malabsorption, and clinical symptoms

Study	Comparison	Outcome	Crude odds Ratio (95% CI)
Dietary preferences as a lifestyle choice			
Black, 2002[32] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Bad taste of milk vs. not	Presence of milk related symptoms	**0.05 (0.01; 0.24)**
	Lifestyle choice: The family consumed soymilk or goat milk rather than cow milk vs. not		0.22 (0.04; 1.21)
	Subjects whose family member avoided cow milk consumption vs. not		1.26 (0.33; 4.84)
Genetic polymorphism			
Obermayer-Pietsch, 2004[25] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 0.55/Y	TT vs. CC	Dislike of milk taste	0.83 (0.25; 2.73)
		Frequency of aversion to milk consumption	**0.26 (0.09; 0.70)**
		Dislike of milk taste	1.54 (0.58; 4.11)
		Frequency of aversion to milk consumption	**0.14 (0.05; 0.39)**
		Dislike of milk taste	0.54 (0.20; 1.43)
		Frequency of aversion to milk consumption	1.80 (0.56; 5.81)
Obermayer-Pietsch, 2007[24] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 349/Y	TT vs. CC	Dislike of milk taste	**0.18 (0.05; 0.63)**
		Aversion to milk consumption	**0.05 (0.01; 0.40)**
Enattah, 2004[7] Country: Finland Young men Ca++ intake difference in comparison groups: /	TT or C/T vs. CC	Self reported lactose intolerance	0.39 (0.09; 1.65)
Gugatschka, 2005[12] Country: Austria Adult males Ca++ intake difference in comparison groups: 5/N	T/T vs. C/C	Self-reported lactose intolerance	1.49 (0.09;2 4.47)
	C/T vs. C/C		2.03(0.22;18.59)
	T/T vs. C/T		0.73(0.08;6.74)
Gugatschka, 2007[13] Country: Austria Elderly male Ca++ intake difference in comparison groups: -7/N	T/T vs. C/C	Self reported Lactose intolerance	1.35 (0.08; 22.12)
	C/T vs. C/C		1.48 (0.15; 14.48)
	T/T vs. C/T		0.91 (0.09; 9.00)
Black, 2002[32] Country: New Zealand Prepubertal children with a history of	Lactose intolerance vs. none	Presence of milk related symptoms	**190.09 (9.92; 3642.28)**
	Consulted a health professional vs. not		**13.50 (3.40; 53.68)**

Appendix Table D4. Association between low lactose diets, lactose intolerance or malabsorption, and clinical symptoms (continued)

Study	Comparison	Outcome	Crude odds Ratio (95% CI)
long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR			
Objectively detected lactose malabsorption			
Goulding, 1999[11] Country: New Zealand Middle age and older women Ca++ intake difference in comparison groups: NR/NR	Malabsorbers vs. absorbers	Symptoms of gastrointestinal discomfort associated with milk intake	2.06 (0.04; 106.52)
Kudlacek, 2002[20] Country: Austria Adults Ca++ intake difference in comparison groups: NR/NR	Moderate lactose malabsorption vs. absorbers	Moderate symptoms (diarrhea, abdominal cramps) during the H2 breath test	1.34 (0.59; 3.01)
	Moderate lactose malabsorption vs. absorbers	Severe symptoms (diarrhea, abdominal cramps) during the H2 breath test	**3.58 (1.43; 9.00)**
	Severe lactose malabsorption vs. absorbers	Moderate symptoms (diarrhea, abdominal cramps) during the H2 breath test	1.66 (0.86; 3.19)
		Severe symptoms (diarrhea, abdominal cramps) during the H2 breath test	**6.22 (2.87; 13.51)**
Di Stefano, 2002[5] Country: Italy Adults Ca++ intake difference in comparison groups: -54/Y	Lactose malabsorption vs. absorbers	Symptoms of LI	**107.98 (6.34; 1838.99)**
Horowitz, 2987[17] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: /	Malabsorbers vs. absorbers	History of milk intolerance	1.50 (0.31; 7.19)
Rockell, 2005[46] Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	Baseline vs. 2 years of followup	Any symptoms related to milk intake were the reason for avoidance	**3.30 (1.33; 8.19)**
		No milk intake whatsoever	**8.95 (3.00;2 6.71)**

Appendix Table D5. Gains in osteodensitometric values in prepubertal boys consuming low lactose diet (74% of the recommended daily Ca++ intake) after interventions with dairy foods (1,607 vs. 747mg/day of Ca++)[53]

Outcome	Outcome Mean ±STD in Active Group	Outcome Mean ± STD in Control Group	Mean Difference (95% CI)
12 months	**Gain in BMD**		
Radial metaphysis	14.6±19.2	11.2±16.7	3.4 (-1.237; 8.037)
Radial diaphysis	25.6±22.2	22.3±19.6	3.3 (-2.096; 8.696)
Femoral neck	22±31.9	22.7±30	-0.7 (-8.674; 7.274)
Femoral trochanter	25±31.3	20.5±27.5	4.5 (-3.092; 12.092)
Femoral diaphysis	76.3±31.7	64.3±33	**12 (3.675; 20.325)**
Lumbar spine (L2–L4)	25.9±18	28.1±18.5	-2.2 (-6.897; 2.497)
12 months	**Gain in BMC (mg/year)**		
Radial metaphysis	79±62	71±56	8 (-7.219; 23.219)
Radial diaphysis	93±58	87±46	6 (-7.5; 19.5)
Femoral neck	159±187	164±222	-5 (-57.752; 47.752)
Femoral trochanter	472±198	495±211	-23 (-75.635; 29.635)
Femoral diaphysis	4,460±2234	4,011±2119	449 (-111.669; 1009.669)
Lumbar spine (L2–L4)	1,971±804	1,994±814	-23 (-231.214; 185.214)
Mean of 5 appendicular skeletal sites	1,064±470	969±449	95 (-23.35; 213.35)

Bold - statistically significant difference at 95% confidence level

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Lactose free diet				
Country: Hong Kong Elderly Chinese vegetarian women Ca++ intake difference in comparison groups: -94/Y	vs. lactovegetarians	BMD spine (L1±L4)		0.04 (-0.02; 0.10)
		BMD femoral neck		0.02 (-0.02; 0.06)
		BMD intertrochanteric area		0.00 (-0.06; 0.06)
		BMD ward triangle		0.00 (-0.04; 0.04)
Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: 182/Y	baseline	Total body BMD		**0.04 (0.03; 0.05)**
		33% radius BMD		**0.06 (0.05; 0.07)**
		Lumbar spine (L2–4) BMD		**0.05 (0.03; 0.07)**
		Femoral neck BMD		**0.11 (0.07; 0.15)**
		Hip trochanter BMD		**0.10 (0.07; 0.12)**
		UD radius, z score		-0.35 (-0.61; 0.21)
		33% radius, z score		0.38 (-0.10; 0.67)
		Lumbar spine (L2–4), z score		**-0.22 (-0.39; -0.05)**
		Femoral neck, z score		**0.86 (0.20; 1.51)**
		Hip trochanter, z score		**0.69 (0.23; 1.15)**
		Total body, z score		**-0.28 (-0.40; -0.12)**
Country: New Zealand Prepubertal children with a history of long-term milk avoidance Ca++ intake difference in comparison groups: NR/NR	avoiders vs. reference healthy children	Total-body BMD		0.13 (-0.17; 0.43)
		Femoral neck BMD		**-1.11 (-2.00; -0.22)**
Country: Taiwan Postmenopausal Taiwanese women Ca++ intake difference in comparison groups: NR/NR	practice vs. nonlong-term vegan and nonvegan vegetarians	Lumbar spine BMD		-0.03 (-0.08; 0.01)
		Femoral neck BMD	continuous variable), vigorous physical activity (three categories), calcium, protein, and nonprotein kcal (as continuous variables)	**-0.05 (-0.08; -0.02)**
Country: Estonia Adults Ca++ intake difference in comparison groups: NR/NR	vs. high (>4dL/day)	Femoral BMD (total)		**-0.05 (-0.10; -0.01)**
		Spinal BMD (L1- L4) g/cm^2		**-0.08 (-0.14; -0.01)**
Du, 2002[6] Country: China	No milk consumers vs. low milk group (<22±18 g/day)	BMD (g/cm^2); distal one-third radius	Crude	**-0.03 (-0.04; -0.01)**

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2) (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Ca++ intake difference in comparison groups: NR/NR		Distal one-third ulna		-0.02 (-0.03; 0.00)
		Distal one-tenth radius		**-0.03 (-0.04; -0.01)**
		Distal one-tenth ulna		-0.02 (-0.04; 0.00)
	group (>128±165 g/day)	Distal one-third radius		**-0.04 (-0.05; -0.02)**
		Distal one-third ulna		-0.02 (-0.03; 0.00)
		Distal one-tenth radius		**-0.04 (-0.05; -0.02)**
		Distal one-tenth ulna		**-0.03 (-0.05; -0.02)**
Country: Hong Kong Elderly Chinese vegetarian women Ca++ intake difference in comparison groups: NR/NR	vs. omnivores	BMD (g=cm^2) spine (L1±L4)		0.00 (-0.06; 0.06)
		BMD (g=cm^2) femoral neck		-0.03 (-0.06; 0.00)
		BMD (g=cm^2) Intertrochanteric area		-0.04 (-0.09; 0.01)
		BMD (g=cm^2) ward triangle		**-0.05 (-0.08; -0.02)**
Genetic polymorphism				
Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 0.55/Y		Lumbar BMD		**0.07 (0.01; 0.13)**
		Femoral neck		**0.05 (0.01; 0.09)**
		Total hip		**0.07 (0.02; 0.12)**
		Ward's triangle		**0.06 (0.01; 0.11)**
		Lumbar BMD		0.00 (-0.05; 0.05)
		Femoral neck		0.01 (-0.03; 0.05)
		Total hip		0.03 (-0.01; 0.07)
		Ward's triangle		0.02 (-0.02; 0.06)
		Lumbar BMD		**0.07 (0.03; 0.11)**
		Femoral neck		**0.04 (0.01; 0.08)**
		Total hip		**0.04 (0.00; 0.08)**
		Ward's triangle		**0.04 (0.00; 0.08)**
Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: 349/Y		Lumbar BMD		0.07 (-0.01; 0.15)
		Femoral neck BMD [g/cm^2]		**0.05 (0.00; 0.10)**
		Total hip BMD		**0.07 (0.01; 0.13)**
Country: Finland Young men Ca++ intake difference in comparison groups: NR/NR		Lumbar spine BMD (g/cm^2)		0.05 (-0.49; 0.59)
		Femoral neck BMD (g/cm^2)		0.04 (-0.59; 0.67)
		Trochanter BMD		0.04 (-0.45; 0.53)
		Total hip BMD		0.03 (-0.44; 0.50)
		BMD, lumbar spine	weight, smoking, alcohol consumption and current exercise	0.03 (-0.03; 0.09)
		BMD, femoral neck		0.01 (-0.05; 0.08)
		BMD, total hip		0.02 (-0.04; 0.09)
	C/T vs. C/C	Lumbar spine BMD	Crude	0.01 (-0.60; 0.63)

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2) (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
		Femoral neck BMD		0.01 (-0.50; 0.52)
		Trochanter BMD		-0.01 (-0.56; 0.55)
		Total hip BMD		0.00 (-0.49; 0.50)
		BMD, lumbar spine	weight, smoking, alcohol consumption and current exercise	0.05 (-0.01; 0.10)
		BMD, femoral neck		0.01 (-0.05; 0.08)
		BMD, total hip		0.02 (-0.04; 0.08)
		Lumbar spine BMD		0.04 (-0.50; 0.57)
		Femoral neck BMD		0.03 (-0.59; 0.64)
		Trochanter BMD		0.04 (-0.46; 0.55)
		Total hip BMD		0.03 (-0.45; 0.51)
		BMD, lumbar spine	weight, smoking, alcohol consumption and current exercise	-0.01 (-0.06; 0.03)
		BMD, femoral neck		0.00 (-0.06; 0.06)
		BMD, total hip		0.00 (-0.05; 0.06)
Country: Estonia Adults Ca++ intake difference in comparison groups: NR/NR		Femoral BMD (total)		-0.03 (-0.07; 0.02)
		Spinal BMD (L1- L4)		-0.01 (-0.07; 0.05)
		Femoral BMD (total)		-0.03 (-0.07; 0.01)
		Spinal BMD (L1- L4)		-0.02 (-0.07; 0.03)
		Femoral BMD (total)		0.00 (-0.03; 0.04)
		Spinal BMD (L1- L4)		0.00 (-0.05; 0.05)
		Femoral BMD (total)		0.03 (-0.01; 0.07)
		Spinal BMD (L1- L4)		0.02 (-0.03; 0.06)
Lactose intolerance				
Corazza, 1995[4] Country: Italy Postmenopausal women Ca++ intake difference in comparison groups: -246/Y	Lactose malabsorbers with symptoms of intolerance vs. without symptoms	BMD z score	Crude	**-0.60 (-1.17; -0.03)**
Country: Italy Adults Ca++ intake difference in comparison groups: -240/Y		BMD (T-score): lumbar spine		**-0.98 (-1.32; -0.64)**
		BMD (T-score): femoral neck		**-0.94 (-1.28; -0.60)**
		BMD (z-score): lumbar spine		**-0.90 (-1.24; -0.56)**
		BMD (z-score): femoral neck		**-0.88 (-1.22; -0.54)**
Corazza, 1995[4] Country: Italy Postmenopausal women	Lactose intolerace (clinical diagnosis) vs. not	BMD z score	Crude	0.30 (-0.16; 0.76)

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2) (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Ca++ intake difference in comparison groups: -138/NR				
Country: Estonia Adults Ca++ intake difference in comparison groups: NR/NR	vs. not	Femoral BMD (total) g/cm^2		-0.01 (-0.06; 0.04)
		Spinal BMD (L1- L4) g/cm^2		-0.04 (-0.10; 0.02)
Country: Israel Adults Ca++ intake difference in comparison groups: NR/NR	population; BMD z-Scores	BMD z-Scores: femoral neck in Premenopausal women		0.15 (-0.20; 0.50)
		Hip in premenopausal women		0.25 (-0.01; 0.51)
		L2–L4 in premenopausal women		**-0.59 (-0.96; -0.22)**
		Femoral neck in postmenopausal women		-0.07 (-0.38; 0.24)
		Hip in postmenopausal women		0.04 (-0.28; 0.36)
		L2–L4 in Postmenopausal women		-0.87 (-0.95; -0.79)
		Femoral neck in men		**-0.45 (-0.88; -0.02)**
		Hip in men		-0.45 (-0.92; 0.02)
		L2–L4 in men		**-1.32 (-1.74; -0.90)**
Lactose malabsorption				
Country: Finland Perimenopausal women Ca++ intake difference in comparison groups: -280/Y	tolerance test	Femoral BMD, no fractures	menopausal status, weight, and HRT history	-0.01 (-0.03; 0.01)
		Femoral BMD, wrist fractures		-0.01 (-0.06; 0.04)
		Femoral BMD, ankle fractures		-0.03 (-0.12; 0.06)
		Femoral BMD, tibial fracture		**-0.14 (-0.23; -0.05)**
		Spinal bone BMD, no fractures		-0.01 (-0.03; 0.02)
		Spinal bone BMD, wrist fractures		-0.04 (-0.08; 0.00)
		Spinal bone BMD, ankle fracture		-0.05 (-0.15; 0.05)
		Spinal bone BMD, tibial fracture		-0.08 (-0.17; 0.00)

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2) (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Honkanen, 1996[16] Country: Finland perimenopausal women Ca++ intake difference in comparison groups: -270/Y	Positive vs. negative lactose tolerance test	Femoral BMD	Adjusted for Calcium intake, weight, age, years since menopause, HRT	0.15 (-18.02; 18.32)
	Positive vs. negative lactose tolerance test in premenopausal	Spinal BMD	Crude	0.01 (-0.04; 0.06)
	Positive vs. negative lactose tolerance test in postmenopausal			-0.05 (-0.09; -0.01)
	Positive vs. negative lactose tolerance test in postmenopausal, hormone replacement therapy 6 months or more			-0.08 (-0.12; -0.03)
	Positive vs. negative lactose tolerance test in postmenopausal, no HRT			-0.02 (-0.07; 0.04)
	Positive vs. negative lactose tolerance test in premenopausal			-0.02 (-0.07; 0.04)
	Positive vs. negative lactose tolerance test in postmenopausal			-0.03 (-0.06; 0.00)
	Positive vs. negative lactose tolerance test in postmenopausal, hormone replacement therapy 6 months or more			-0.05 (-0.09; -0.01)
	Positive vs. negative lactose tolerance test in postmenopausal, no HRT			-0.01 (-0.06; 0.04)
Country: Italy Adults Ca++ intake difference in comparison groups: -54/Y		BMD (T-score): lumbar spine		-0.22 (-0.49; 0.05)
		BMD (T-score): femoral neck		-0.21 (-0.48; 0.06)
		BMD (z-score): lumbar spine		-0.25 (-0.52; 0.02)
		BMD (z-score): femoral neck		-0.22 (-0.49; 0.05)
Corazza, 1995[4] Country: Italy Postmenopausal women Ca++ intake difference in comparison groups: -2/N	Lactose malabsroption vs. no	BMD z score	Crude	-0.30 (-0.77; 0.17)
Country: Finland Adults	Malabsorbers vs. absorbers (men only)	Mineral density distal radius		0.01 (-0.02; 0.03)
	Malabsorbers vs. absorbers	Mineral density distal		0.03 (0.00; 0.05)

Appendix Table D6. Association between lactose intake and metabolism and bone mineral density (BMD, g/cm^2) (continued)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Ca++ intake difference in comparison groups: NR/NR	(women only)	radius		
Country: Austria Adults Ca++ intake difference in comparison groups: NR/NR	Moderate lactose malabsorption vs. no	DEXA (radial) (g/cm^2)		-0.01 (-0.19; 0.17)
	Severe lactose malabsorption vs. no	DEXA (radial)(g/cm^2)		-0.07 (-0.29; 0.15)
	Severe lactose malabsorption vs. moderate	DEXA (radial)(g/cm^2)		-0.06 (-0.21; 0.09)
Horowitz, 1987[17] Country: Austria Postmenopausal women Ca++ intake difference in comparison groups: NR/NR	Lactose malabsroption vs. no	BMD of the right forearm, mg/ml	Crude	-17.00 (-61.44; 27.44)
Country: Finland Adults Ca++ intake difference in comparison groups: NR/NR	only)	Bone mineral linear density (g/cm), distal radius		0.00 (-0.17; 0.17)
		Bone mineral linear density (g/cm), midshaft radius		0.06 (-0.09; 0.21)
		Bone mineral linear density (g/cm), midshaft ulna		0.02 (-0.12; 0.16)
	Malabsorbers vs. absorbers (women only)	Bone mineral linear density (g/cm), distal radius		0.03 (-0.10; 0.16)
		Bone mineral linear density (g/cm), midshaft radius		0.02 (-0.08; 0.12)
		Bone mineral linear density (g/cm), midshaft ulna		0.03 (-0.05; 0.11)

Bold – statistically significant

Appendix Table D7. Association between lactose intake and metabolism and bone density (BD)

Study Difference in Daily Ca++ Intake in Comparison Groups	Comparison	Outcome	Estimate	Mean Difference (95% CI)
Honkanen, 1996[16] Country: Finland Perimenopausal women Ca++ intake difference in comparison groups: -270/Y	Positive vs. negative lactose tolerance test	Spinal BD, mg/cm	Adjusted for calcium intake, weight, age, years since menopause, HRT	**28.27 (3.73; 52.81)**
Gugatschka, 2007[13] Country: Austria Elderly male Ca++ intake difference in comparison groups: -221/Y		Spinal BD (L1–L4) Z score		0.02 (-0.55; 0.59)
		Femoral BD (total) Z score		-0.13 (-0.48; 0.22)
		Femoral BD (neck) Z score		-0.14 (-0.47; 0.19)
		Femoral BD (trochanteric) Z score		-0.26 (-0.62; 0.10)
		Spinal BD (L1–L4) Z score		-0.07 (-0.68; 0.54)
		Femoral BD (total) Z score		-0.17 (-0.56; 0.22)
		Femoral BD (neck) Z score		-0.02 (-0.38; 0.34)
		Femoral BD (trochanteric) Z score		-0.27 (-0.67; 0.13)
Gugatschka, 2005[12] Country: Austria Adult males Ca++ intake difference in comparison groups: -3/N		Spinal BD (L1–L4) Z score		0.41 (-0.11; 0.92)
		Femoral BD (total) Z score		0.04 (-0.27; 0.34)
		Spinal BD (L1–L4) Z score		0.29 (-0.26; 0.83)
		Femoral BD (total) Z score		0.01 (-0.33; 0.34)
		Spinal BD (L1–L4) Z score		-0.12 (-0.49; 0.26)
		Femoral BD (total) Z score		-0.03 (-0.27; 0.21)
Gugatschka, 2007[13] Country: Austria Elderly male Ca++ intake difference in comparison groups: 14/N		Spinal BD (L1–L4) Z score		-0.09 (-0.49; 0.31)
		Femoral BD (total) Z score		-0.04 (-0.31; 0.23)
		Femoral BD (neck) Z score		0.12 (-0.16; 0.40)
		Femoral BD (trochanteric) Z score		-0.01 (-0.31; 0.29)

Bold – statistically significant

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 3 and 4

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
A. Commercially-available lactase/lactose hydrolysed milk, or non-lactose solutions						
Montalto, 2005[54] RCT, crossover Sponsorship: not reported Italy Duration of symptom recording: 8 hours	Data source: 30 Italian subjects referred because of symptoms compatible with lactose intolerance with a positive lactose H2 breath test. Each patient underwent, in a random order, three H2 breath tests. An interval of at least 72 hours was allowed among successive tests (20 g lactose), to avoid the effect of colonic acidification. Inclusion criteria: Symptoms compatible with lactose intolerance. Methods to measure outcomes: Subjects kept a diary where they recorded occurrence of intolerance symptoms for 8 hours following milk ingestion.	Mean age (range): 43 (18-65) Gender: women 63%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	β-d-galactosidase from *Kluyveromyces lactis* 1) Test A -enzyme (3000 UI) added to 400 mL milk (lactose content 20 g) 10 h before milk consumption x 1 dose 2) Test B-enzyme (6000 UI) added 5 min before 400 mL milk (lactose content 20 g) consumption x 1 dose	Placebo before 400 mL milk (lactose content 20 g) plus aspartame (to simulate the taste of lactase-treated milk x 1 dose	Clinical score based on symptoms whose severity was indicated by a score for each symptom (0=absent; 1=mild; 2=moderate; 3=severe). Conclusion(s): A significant reduction of the mean clinical score after both test A (0.36 ± 0.55) and test B (0.96 ± 0.85) versus placebo (3.77 ± 0.79) (P<0.001). There was also a significant reduction after Test A versus Test B (P=0.03).	Allocation concealment: adequate (numbered containers, identical in shape and color) Blinding: double + analysis by a blinded statistician. Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Gremse, 2003[55] RCT, crossover Sponsorship: not reported USA Duration of symptom recording: 2 weeks	Data source: 30 American child subjects with lactose mal-digestion a positive lactose H2 breath test. Inclusion criteria: Recurrent abdominal pain of childhood with at	Mean age (range): 11 (3-17) Gender: women 63%. Race/ethnicity: black 53%, white 47%. Comorbidities: not	240 mL Lactose-free milk (LFM) to which lactase 2 g from *Kluyveromyces lactis* (Lactaid, Pleasantville, NY) was added to 2%	240 mL Milk (lactose content 12 g) 2% homogenized milk plus aspartame (to simulate the taste of lactase-treated milk) taken for 14	Symptom scores for the 14 day period (mean ± SEM). Severity of symptoms was graded as: 0=none; 1=trivial, 2=mild; 3= moderate; 4=severe. Sum of the	Allocation concealment: unclear Blinding: Double Intent-to-treat analyses: 100% followup Study withdrawals

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	least 3 discrete episodes of abdominal pain severe enough to affect daily activities for 3 months or more. Exclusion criteria: Organic causes of abdominal pain. Methods to measure outcomes: Subjects and/or their parents recorded their symptoms daily in a diary that was collected at weekly intervals during each study period.	reported Cointerventions: not reported	homogenized milk (lactose content 12 g) taken for 14 days (2 week washout period)	days	individual symptom scores was calculated for each 14-day study period and averaged for all subjects. Significant increase in abdominal pain during the lactose ingestion period compared to the lactose-free period. Conclusion(s): Authors conclude that ingestion of 12 g of lactose daily is associated with increased abdominal pain in susceptible children with lactose maldigestion.	adequately described: no withdrawals reported
Järvinen, 2003[56] RCT, crossover Sponsorship: not reported Finland Duration of symptom recording: 8 hours	Data source: 27 Finnish subjects who had experienced gastrointestinal symptoms after consuming milk or food containing lactose. Inclusion criteria: lactose maldigestion based on rise in blood glucose <1.1 mmol/l within 1 hour after ingesting 50 g lactose dissolved in water. Methods to measure outcomes: Gastrointestinal symptoms including	Students and staff at a university. No further information provided.	100 g chocolate sample consisting of lactose-free milk powder.	100 g chocolate sample consisting of low-lactose milk powder (lactose content 2 g). 100 g chocolate sample consisting of whole milk powder (lactose content 12 g). 100 g chocolate sample consisting of whole milk (lactose content 12 g). The chocolate sample was eaten in the morning	Number of subjects reporting symptoms and mean symptom scores for individual gastrointestinal symptoms. Conclusion(s): Numbers of subjects reporting GI symptoms did not differ significantly after eating chocolate samples.	Allocation concealment: unclear Blinding: described as "blinded," no further details. Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	flatulence, abdominal bloating, abdominal pain, borgorygmi and nausea were recorded on a questionnaire with a scale ranging from 0 (no symptoms) to 10 (very severe symptoms disturbing normal life) once every hour for the first 3 hours and then two more times (at 4-6 and 7-8 hours) until 8 hours had elapsed since the test meal.			between 8 and 10 o'clock after an overnight fast		
Suarez, 1998[57] RCT, crossover Sponsorship: Department of Veteran Affairs, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Dairy Council. USA Duration of symptom recording: 1 week	Data source: 31 American women subjects with lactose maldigestion a positive lactose H2 breath test plus 31 American women digester controls. Inclusion criteria: Lactose maldigestion based on an increase in the breath-hydrogen concentration of >0.45 mmol/L (10 ppm) after the oral ingestion of a 250-mL aqueous solution containing 15 g lactose (0.18 mol/L) was used as the indicator of lactose maldigestion. Exclusion criteria: Previously had gastrointestinal surgery,	Maldigestion group (n=31): Mean age 46.9 ± 2.6 y Gender: women 100%. Race/ethnicity: Asian 29%; Hispanic 16%; black 6%; white 45%, of whom 4 were Jewish Digestion group Mean age 49.4 ±2.4 Gender: women 100%. Race/ethnicity: white 100% Prior to the study, 23 women in the lactose mal-digestion group	Lactose hydrolyzed products (LHP), lactose totaling 34 g daily. The lactose in fresh, low-fat milk was hydrolyzed by adding 1.07 g of a lactase preparation obtained from *Kluyveromyces lactis* 240 mL lactose hydrolyzed,1%-fat milk with breakfast and dinner; 1 serving (28 g) of a hard cheese at lunch and at dinner; and 240 mL low-fat, strawberry flavored, lactose-hydrolyzed yogurt at lunch. Subjects ingested	Conventional diary products (CDP) lactose totaling 34 g daily. 240 mL conventional, 1%-fat milk with breakfast and dinner; 1 serving (28 g) of a hard cheese at lunch and at dinner; and 240 mL (8 oz) lowfat, strawberry-flavored yogurt at lunch time	Severity of symptoms, (Mean ± SEM), ranked on a continuous scale from 0 to 5 as follows: 0 (no symptoms), 1 (trivial), 2 (mild), 3 (moderate), 4 (strong), or 5 (severe symptoms). Women with lactose maldigestion reported significantly increased flatus frequency and subjective impression of rectal gas during the period of high lactose intake; however, bloating, abdominal pain, diarrhea, and the global perception of overall symptom	Allocation concealment: unclear Blinding: Double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	had significant intercurrent illnesses, had received antibiotic therapy within the past 2 months, or allergy to aspartame, milk, yogurt, or cheese. Methods to measure outcomes: The occurrence and severity of symptoms (bloating, abdominal pain or cramps, and subjective impressions of rectal gas excretion) were self-rated by subjects on 2 occasions daily (for the periods from breakfast time to dinnertime and from dinnertime to bedtime) during the baseline and the 2 test periods.	and 2 in the lactose digestion group believed that the ingestion of dairy products resulted in appreciable abdominal symptoms.	their regular diets with the exception of the additional dairy products. The dairy products provided <1300 mg Ca/d; it was assumed that the remainder of the diet provided <200 mg.		severity were not significantly different between the 2 treatment periods. Conclusion(s): Authors conclude that the symptoms resulting from lactose maldigestion are not a major impediment to the ingestion of a dairy-rich diet supplying <1500 mg Ca/day.	
Xenos, 1998[58] RCT, crossover Sponsorship: not reported Greece Duration of symptom recording: 1 day	Data source: 8 Greek lactose intolerant volunteers. Inclusion criteria: Rise in blood glucose levels <1.1 mmol/L above fasting level after ingestion of lactose (1 g/kg of body weight) and if intestinal symptoms occurred. Methods to measure outcomes: Subjects completed questionnaire regarding	Mean age 32 No other data were provided.	Lactose treatment: β-D-galactosidase 100 u/mL + 100 g lactose dissolved in water. There was a washout period of 1 week between challenges.	Matching placebo + 100 g lactose dissolved in water.	Subjects reporting symptoms based on ratings (0=none to 4=severe), 8 hours after lactose challenge. Conclusion(s): Subjective ratings of the severity of symptoms (cramps, belching, flatulence, diarrhea) were significantly decreased with the lactose treatment	Allocation concealment: unclear Blinding: Double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	symptoms 8 hours after consuming tests and then every 8 hours until 24 hours elapsed. Symptoms were rated from 0=none to 4=severe.				compared to placebo.	
Suarez, 1997[59] RCT, crossover Sponsorship: Department of Veteran Affairs, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Dairy Council. USA Duration of symptom recording: 1 week	Data source: 19 American symptomatic lactase-nonpersistent (S-LNP) subjects self-described as "severely lactose intolerant," plus 13 LNP subjects who denied lactose intolerance (A-LNP), and 10 lactase-persistent subjects who believed they were lactose intolerant (S-LP). Inclusion criteria: Individuals who reported GI symptoms after one cup of milk. Lactose maldigestion based on an increase in the breath-hydrogen concentration of >10 ppm after the oral ingestion of a 250-mL aqueous solution containing 15 g lactose was used as the indicator of lactose malabsorption, hence LNP. Exclusion criteria:	S-LNP Group (n=19) Mean age 34 ±22 years (range 18-43) Gender: women 53%. Race/ethnicity: Asian 63%; black 11%; Hispanic 5%; white 21% A-LNP Group (n=13) Mean age 35.9 ±11 years (range 25-69) Gender: women 38%. Race: Asian 69%; black 8%; Hispanic 15%; white 8% S-LP Group (n=10) Mean age 35.9 ±11 years (range 25-69) Gender: women 38%. Race/ethnicity: Asian 69%; black 8%; Hispanic 15%; white 8%	240 mL lactose hydrolyzed milk (lactose totaling 11.8 g, 23.6 daily), consumed at breakfast and dinner. The lactose in fresh, low-fat milk was hydrolyzed by adding 1.07 g of a lactase preparation obtained from *Kluyveromyces lactis* to 1 L milk. A washout period of 7 days between treatments.	240 mL regular milk (lactose totaling 11.8 g, 23.6 daily), plus aspartame (to simulate the taste of lactase-treated milk, consumed at breakfast and dinner.	Mean symptom severity scores ranked scale on a scale as follows: 0=none; 1=trivial; 2= mild; 3=moderate; 4= strong; 5= severe. *Extracted from graph* Neither LNP group had a significant increased in symptoms during the regular milk period compared to the lactose hydrolyzed milk period. S-NLP subjects reported significantly greater gaseous symptoms compared to A-NLP during both feeding periods. Conclusion(s): Authors concluded lactase-nonpersistent subjects can tolerate two cups of milk per day without appreciable symptoms.	Allocation concealment: unclear Blinding: Double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	Inconsistent GI symptoms (bloating, abdominal pain, flatulence, or diarrhea), prior gastrointestinal surgery or other significant illnesses, received antibiotic therapy within the past 2 months, or inability to consume aspartame. Methods to measure outcomes: Subjects rated symptoms (bloating, borborygmi, abdominal pain or cramps, and subjective impressions of rectal gas excretion) on 4 occasions daily (morning, noon, afternoon, night) during the baseline and the 2 test periods. Subjects also recorded diarrhea, and each passage of flatus.					
Vesa, 1997[60] RCT, crossover Sponsorship: Finnish Association of Agronomists Finland Duration of symptom recording: 2 days	Data source: 30 Estonian subjects with lactose maldigestion. Inclusion criteria: Lactose maldigestion based on measuring of urinary galactose concentration after ingesting 50 g lactose with 150 mg ethanol/kg body weight, with	Mean age (range): 46 (18-74) Gender: women 90%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	200 mL lactose-free milk (0.1% fat) x 2 daily (lactose totaling 0 g over 2 days)	200 mL fat-free milk (0.1% fat) x 2 daily, (lactose totaling 19.6 g over 2 days) 200 mL high-fat milk (4.9% fat) x 2 daily (lactose totaling 19.6 g over 2 days) Milk-free period over 5 days	Percentage of subjects who experienced symptoms during the test day after each lactose dose The sum of symptoms was higher during all milk periods than during the milk-free period (P<0.01).	Allocation concealment: unclear Blinding: Double blinding attempted, although it was noted that full fat milk can be readily discerned from fat-free milk.

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	symptom followup during the test day. Exclusion criteria: No gastrointestinal diseases, were not on medications, on antibiotics at least two months prior to study, or had irritable bowel syndrome. Methods to measure outcomes: On test days, after consuming milk, subjects noted symptoms (flatulence, nausea, abdominal bloating, abdominal pain) on a questionnaire with a visual analog scale (VAS).				There were no statistically significant differences in the occurrence or severity of symptoms during the fat-free milk period compared with the high-fat milk period. Conclusion(s): A marked difference in the fat content of milk did not affect the symptoms of lactose intolerance.	Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Vesa, 1996[61] RCT, crossover Sponsorship: not reported Finland Duration of symptom recording: 1 day	Data source: 39 Finnish subjects with lactose maldigestion and 15 lactose digesters. Inclusion criteria: Lactose maldigestion based on a positive lactose H2 breath test (39%) or lactose tolerance test with ethanol (61%). Lactose maldigesters who experienced at least moderate gastrointestinal symptoms, i.e., loose stools, abdominal pain, abdominal bloating, or	1. Lactose mal-digesters (n=39) Mean age (range): 47.2 (27-70) Gender: women 62%. Race/ethnicity: white 100%. 2. Lactose digesters (n=15) Mean age (range): 38.3 (25-54) Gender: women 66%. Race: white 100%. Comorbidities: 5 hypertensives and one diabetic.	200 mL fat-free, lactose-free milk x 1 serving (lactose was separated chromatograph-ically). The taste of the milk was disguised with 0.2 g lemon flavoring and the sweetness and osmolarity of the test milks were equalized with glucose.	200 mL fat-free, lactose-free milk x 1 serving (lactose was separated chromatograph-ically) plus 0.1% /3-galactosidase was added to ensure that it contained no traces of lactose. Milk 1. plus 0.5 g lactose Milk 2. plus 1.5 g lactose Milk 3. plus 7 g lactose	Percentage of subjects who experienced symptoms during the test day after each lactose dose. Maldigesters reported significantly more abdominal bloating and abdominal pain than the digesters. There was no difference in the mean severity of the reported symptoms between the test milks and the lactose-free milk in the group of	Allocation concealment: unclear Blinding: Double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	flatulence, were selected for in the study group. Exclusion criteria: No gastrointestinal diseases or on antibiotics one month prior to study. Methods to measure outcomes: On test, for 12 h after consuming milk, subjects noted symptoms (flatulence, abdominal bloating, abdominal pain, borborygmi, and loose stools) on a questionnaire with a visual analog scale (VAS)	Cointerventions: not reported			lactose maldigesters, of whom one-third did not experience any symptoms from any of the test doses. The same proportion (64%) of the maldigesters experienced symptoms after both the lactose-free milk and the milk with 7 g lactose. Conclusion(s): Gastrointestinal symptoms in most lactose maldigesters are not induced by lactose when small amounts (0.5-7.0 g) of lactose are included in the diet.	
Saurez, 1995[62] RCT, crossover Sponsorship: Department of Veterans Affairs, National Institute of Diabetes and Digestive and Kidney Diseases, and the University of Minnesota USA Duration of symptom recording: 1 week	Data source: 30 American subjects who reported severe lactose intolerance with consistent related symptoms. Subjects were classified as having lactose mal-absorption if their breath H2 concentrations increased by more than 10 parts per million (ppm) (0.93 x 10^{-6} g of H2 per liter of air or 0.45 µmol per liter). The ability of the colonic	*Lactose mal-absorbers (n=21)* Mean age (range): 29.4 (18-50) Gender: women 62%. Race/ethnicity: white 38%; Asian 33%, Hispanic 24%; black 5%. *Lactose absorbers (n=9, those with increase in H2 <10 ppm)* Mean age (range): 25.1(18-45)	Hydrolyzed low-fat milk (HM) (lactose content <0.05 g) by adding 1.07 g of lactase from *Kluyveromyces lactis* (Lactaid, Pleasantville, NY) to 1 liter of milk at breakfast daily for a one-week period.	Low-fat milk (lactose content 12.1 g) to plus aspartame (to simulate the taste of lactase-treated milk) at breakfast daily for a one-week period.	Intensity of daily gastrointestinal symptoms over the one week period (mean ± SEM), 0=none; 1=trivial; 2=mild; 3=moderate; 4=strong symptoms; and 5=severe. Diarrhea or loose stool was defined as "an urgent, watery defecation." In Subjects recorded each passage of flatus.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	flora to produce hydrogen through fermentation in response to carbo-hydrate malabsorption was tested in seven of the nine subjects who were able to absorb lactose after they ingested 10 g of lactulose. Exclusion criteria: Subjects were excluded if they did not report consistently having symptoms after drinking less than 240 ml of milk; if they had undergone gastro-intestinal surgery, had other major illnesses, or received antibiotic therapy within the previous two months; or if they indicated that they could not consume aspartame. Methods to measure outcomes: Subjects rated the occurrence and severity of gastro-intestinal symptoms experienced during the 24-hour period after each test meal.	Gender: women 56%. Race/ethnicity: white 89%; East Indian 11% Comorbidities: not reported Cointerventions: not reported.			During the study periods, gastrointestinal symptoms were minimal. When the periods were compared, there were no statistically significant differences in the severity of these four gastrointestinal symptoms. Conclusion(s): People who identify themselves as severely lactose-intolerant may mistakenly attribute a variety of abdominal symptoms to lactose intolerance. When lactose intake is limited to the equivalent of 240 ml of milk or less a day, symptoms are likely to be negligible and the use of lactose-digestive aids unnecessary.	
Johnson, 1993[63] RCT, crossover Sponsorship: The	Data source: 45 lactose-maldigesting and lactose intolerant	Ages ranged from 12-40 in the eligible population.	315 mL hydrolyzed milk (lactose content 0 g) by	315 mL milk (lactose content 16.4 g) plus	Presence of symptoms consistent with lactose mal-	Allocation concealment: unclear

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
National Dairy Board In cooperation with the National Dairy Council USA Duration of symptom recording: unclear	African Americans. All subjects claimed to have GI symptoms after consuming one cup of milk or less. Inclusion criteria: Subjects who had an increase in hydrogen concentration from baseline of ≥ 20 ppm. Exclusion criteria: Chronic constipation and other GI problems, regular cigarette smokers, and subjects on antibiotic therapy. Methods to measure outcomes: Subjects were to record symptoms after ingestion (time period unclear)	Gender: not reported but mostly female (70%) in the eligible population. Race/ethnicity: black 100% Comorbidities: not reported Cointerventions: not reported	adding 30 drops of lactase (Lactaid, Pleasantville, NY) to of milk. Subjects took 3 samples, either HM twice and M once or the opposite on 3 different days, assigned in a random order.	artificial sweetener (to simulate the taste of lactase-treated milk) Subjects took three samples, either M twice and HM once or the opposite on 3 different days, assigned in a random order.	absorption. 33% (n=10) reported symptoms consistent with lactose mal-absorption with both HM and milk. Conclusion(s): Authors conclude that the cause of milk intolerance in up to 1/3rd African Americans claiming symptoms after ingestion of a moderate amount of milk cannot be due to its lactose content.	Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Lin, 1993 Study 2[64] RCT, crossover Sponsorship: Thompson Medical Co., Inc. and the Minnesota Agricultural Experiment Station USA Duration of symptom recording: 8 hours	Data source: 11 American adults similarly characterized as maldigesters as in Study 1 by breath hydrogen analysis following a 50-g lactose load and by past experience with intolerance symptoms following the consumption of dairy foods Inclusion and exclusion criteria: Same as Study 1. Methods to measure	Age range: 18-60 Gender: women 91%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	50 g of lactose dissolved in 200 ml of water plus β-galactosidase (β-gal) enzyme preparations 1) Lactogest soft gel capsules x 2 (Thompson Medical Inc, New York, New York), 2) Lactogest capsules x 4 3) Lactaid caplets x 2 (Lactaid Inc, Pleasantville, New	50 g of lactose dissolved in 200 ml of water plus two soft gel vitamin E capsules containing 420 rag/capsule of α-tocopherol in soybean oil as a Placebo (Pharmacaps Inc, Elizabeth, New Jersey)	Symptom scores, expressed as the sum of mean scores rating symptoms from 1 (none) to 5 (worst ever experienced) at baseline and 4 and 8 hours after challenge. Conclusion(s): Symptom scores for bloating, cramping, nausea, pain, diarrhea, and flatus were not significantly different between treatments and the	Allocation concealment: adequate (small brown coded envelopes) Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported Funding: Some industry support

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	outcomes: Subjects kept a similar diary to Study 1, except that symptoms of bloating, abdominal cramps, nausea, abdominal pain, diarrhea and gas were self-scored by subjects at baseline and 4 and 8 hr on a 1-5 scale (none to worst ever experienced).		Jersey) or 4) DairyEase chewable tablets x 2 (Glenbrook Laboratories, New York, NY)		control.	
Nielsen, 1984[65] RCT, crossover Sponsorship: Danish Medical Research Council Denmark Duration of symptom recording: 1 day	Data source: 9 lactose intolerant Danish children Inclusion criteria: Subjects had to fulfill two of the following: 1) An increase in blood glucose during a lactose tolerance test (2 g of lactose per kilogram of body weight); 2) Diarrhea, borborygmus, and/or flatulence during a lactose tolerance test; 3) Low or no lactase activity in an intestinal biopsy specimen taken at the ligament of Treitz. Exclusion criteria: Subjects with acute or chronic diarrhea or other GI orders. Methods to measure outcomes: At 10 times during the 24 test	Median age (range): 10 (9-16) Gender: female 33%. Ethnicity: 6 subjects immigrants from Korea, Pakistan, or Turkey (plus 3 native Danes) Comorbidities: No subjects had renal or endocrine disorders or hereditary diseases. Cointerventions: None received any medicine during the period of examination.	One half liter of hydrolyzed milk (HM) (lactose content 1.25 g) by adding 2 mL of lactase from *Kluyveromyces fragilis* (Lactozym 3000 L, Novo Industri A/S, Bagsvaerd, Denmark), given after 8 hours of fasting	One half liter of ordinary milk (lactose content 25 g) given after 8 hours of fasting	Summation of observed symptoms from the scoring charts of the 9 subjects. Conclusion(s): Children had significantly fewer clinical symptoms and signs within 24 hours after consuming lactose-hydrolyzed milk compared to regular milk.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported Funding: non-industry

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	periods, a 0 was recorded in the scoring chart to indicate no symptoms and a 1 was recorded if symptoms or defecation was observed by the children's parents.					
Lybeck Sørensen, 1983[66] RCT, crossover Sponsorship: Not reported Denmark Duration of symptom recording: 8 hours	Data source: 35 symptomatic lactose intolerant Danish adults from Latin America. Inclusion criteria: Lactose intolerance based on a lactose tolerance test (not defined), with no known disorders of the gastrointestinal tract. Exclusion criteria: lactose tolerance Methods to measure outcomes: Subjects completed questionnaire concerning the development of symptoms (borbo-rygmus and meteorism, colic attacks, flatulence, and/or diarrhea) based on the following: 0=no symptoms; 1=slight; 2=moderate; 3=severe. The total symptom score was calculated as the sum of the score for each person.	Mean age (range): 32 (20-60) Gender: women 54%. Race/ethnicity: Latin American 100% Comorbidities: not reported Cointerventions: not reported	250 and 500 mL low-lactose milk (lactose content 1.6 g), 86% of the lactose was removed by ultrafiltration and replaced with the addition of malto-dextrose. 48 hours between tests.	250 and 500 mL skim milk (SM) (lactose content 11.3 g).	Frequency of symptoms in percent following milk ingestion. Conclusion(s): Ingestion of 500 mL low-lactose milk resulted in significantly fewer symptoms compared to regular skim milk. After ingestion of 250 mL low-lactose milk there was a tendency to fewer symptoms but the difference was not statistically significant.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
Rask Pedersen, 1982[67] RCT, crossover Sponsorship: NOVO Industries supplied the lactase and performed the HPLC analyses Denmark Duration of symptom recording: 1 day	Data source: 11 symptomatic lactose intolerant Danish adults. Inclusion criteria: Rise in blood glucose levels <1.4 mmol/L above fasting level after ingestion of 50 g lactose with symptoms (abdominal cramp, meteorism, and/or diarrhea). Methods to measure outcomes: On a 24 hour diary sheet, subjects reported abdominal symptoms based on the following. 0=none; 1= mild/moderate; 2= severe. For diarrhea, No diarrhea=formed stools; mild/moderate= ≤3 liquid/soft stools; severe= ≥4 liquid/soft stools.	Mean age: 43 Gender: women 64%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	500 mL low-lactose milk (lactose content 3.75 g), 85% hydrolyzed by adding 2 mL of lactase from *Kluyveromyces fragilis* (Lactozym 3000 L, Novo Industri A/S, Bagsvaerd, Denmark) to of milk x 1 dose.	500 mL ordinary milk (lactose content 25 g), x 1 dose.	Number of subjects reporting symptoms after ingestion Conclusion(s): There was a significant reduction in abdominal symptoms after ingestion of lactose-hydrolyzed milk compared to regular milk.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Reasoner, 1981[68] RCT, crossover Sponsorship: University of Rhode Island and Shadow Research Foundation, Inc. USA Duration of symptom recording: 1 week	Data source: 9 symptomatic American adults from an outpatient clinic and 5 milk tolerant controls. Inclusion criteria: Subjects with a blood sugar <20 mg/100 mL after ingestion of 50 g lactose and had symptoms when challenged with 250 mL of skim milk.	*"Milk-intolerant" (n=9)* Mean age (range): 41 (22-60) Gender: women 44%. Race/ethnicity: not reported Comorbidities: 2 subjects had LI due to Crohn's disease (one also had an intestinal	Low-lactose milk (lactose content ~2.9 g/d) x 1 week), 74-91% hydrolyzed with lactase (Maxilact 40,000, GB Fermentation, Des Plains, Illinois). Average weekly consumed was 1.79 L.	1) Skim milk (lactose content ~28.5 g/d) x 1 week. Average weekly consumed was 1.58 L. 2) Skim milk + glucose (simulates the taste of lactase-treated milk) x 1 week. Average weekly consumed was 1.8 L.	Abdominal symptom responses trans-formed into a numerical value. Numbers correlate with the following: 0 to 0.33 = none to mild; 0.34 to 0.66 = moderate; 0.67 to 1.0 = severe. Conclusion(s): Lactose-hydrolyzed milk significantly	Allocation concealment: unclear Blinding: double Intent-to-treat analyses:100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	Methods to measure outcomes: Subjects rated the occurrence and severity of gastro-intestinal symptoms experienced during the 24-hour period after each test meal. 0=none; 1= mild; 2=moderate; and 3=severe. Number of days that the subject responded per week was totaled. A quotient was then calculated, giving a symptom index for the week.	resection), and one subject had a subtotal gastrectomy. Cointerventions: not reported *"Milk-tolerant" (n=5)* Mean age (range): 33 (22-48) Gender: women 60%. Race/ethnicity: not reported		3) Sweet acidophilus milk x 1 week. Average weekly consumed was 1.50 L.	reduced pain and gas symptoms in the *"Milk-intolerant"* group compared to regular skim milk.	
Unger, 1981[69] RCT, crossover Sponsorship: not reported USA Duration of symptom recording: 1 day	Data source: 24 American lactose malabsorbers (determined by breath hydrogen test) and 75 lactose absorbing adolescent volunteers. Subjects were to report all symptoms during breath hydrogen test period. Presence of ≥1 GI symptom was considered a positive response to lactose. Methods to measure outcomes: Symptomatology questionnaires were given to subjects each day after the test beverage was consumed. One or more	Mean age (range): 24 (18-46) Gender: women 49%. Race/ethnicity: white 87% (northern European n=65; southern-European n=8; Jewish n=14), Asian 10%, black 3%.	240 or 480 mL lactose-free chocolate dairy drink.	240 or 480 mL lactose-containing (lactose content 10.8-21.6 g) chocolate dairy drink.	Subjects reporting symptoms during 24 hours after consumption. Conclusion(s): 12.5% of lactose malabsorbers were symptomatic after consuming 240 mL of lactose-free solution versus 33.3% after consuming 240 mL lactose solution.	Allocation concealment: Blinding: double Intent-to-treat analyses: Study withdrawals adequately described:

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	relevant symptoms occurring between one and 24 hours indicated a positive response to the dairy drink for that test day. The 4 symptoms (bloating, flatulence, cramps, diarrhea) indicative of lactose intolerance were rated according: 0=none; 1=mild; 2=moderate; 3=severe					
Cheng, 1979[70] RCT, crossover Sponsorship: Chile Foundation Chile Duration of symptom recording: 1 day	Data source: Chilean volunteers from the Santiago penitentiary. 15 were lactose intolerant and 16 were lactose tolerant controls. Inclusion criteria: Lactose intolerance, determined by blood glucose analysis [<20 mg/ 100 considered deficient lactase activity] and developed symptoms after ingestion of 50 g lactose. Methods to measure outcomes: A standard questionnaire was applied twice daily. All symptoms, attributable or not to lactose intolerance, were recorded. No symptoms = 0, mild (symptoms	Lactose intolerant subjects (n=15) Mean age (range): 27 (19-34) Gender: men 100% Race/ethnicity: Latin American 100%. Lactose tolerant subjects (n=16) Mean age (range): 27 (18-38) Gender: men 100% Race/ethnicity: Latin American 100%. Comorbidities: not reported Cointerventions: not reported	500 mL low lactose milk (lactose content 0.5 to 1.25 g), hydrolyzed with lactase (galactosidase, Maxilact, Enzyme Development Corporation, New York, NY), x 2 daily for 1 month.	500 mL skim milk (lactose content 25 g), sweetened with sucrose to imitate taste of low-lactose milk. All subjects received at least 4 of these tests.	Results are expressed as the number of times a score was given to each symptom during the experiment. Conclusion(s): Lactose intolerant subjects had more symptoms and more severe symptoms with skim milk.	Allocation concealment: unclear Blinding: noted as double, unclear if milks were given out randomly. Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	present but not interfering with daily activities or <2 liquid bowel movements) = 1, severe (symptoms present and interfering with daily activities or caused great discomfort or >2 liquid bowel movements) = 2. No data on statistical analyses.					
Jones, 1976 Study 2[71] Single blind RCT no masking to taste, crossover USA Duration:8 hours Funded by National Dairy Council and NY State Agriculture Experiment station hatch project	Data Source: 17 American volunteers who reported symptoms after ingesting 25 g lactose but not after placebo. Inclusion criteria: LI on basis of rise in blood glucose of less than 25 mg/100mL after 50 g lactose injection	Mean age 24 (range 20-34) Gender: women 41% Race/ethnicity: Asian 41%; black 18%; Latin-American 12%; Other 29% Comorbid: none Co-intervention: none	60% reduced skim milk 500 ml (10 g lactose) 60% reduced lactose whole milk 500 ml (10 g lactose). Placebo 250 ml (saccharin, lemon juice water)	Regular skim milk 500 ml (25 g lactose). Regular whole milk 500 ml (25 g lactose)	Sum of score of bloating, gas, cramps and diarrhea on scale: 0-none, 1=mild, 2= moderate, 3=severe. Conclusion(s): 1) Lower lactose milk better tolerated; 2.) No differences in tolerance between test beverages	Allocation concealment: unclear Blinding: single no masking Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Studies in which subjects were not noted to be symptomatic at baseline or symptoms were not required for study inclusion (based on biochemical measures only)						
Lin, 1993 Study 1[64] RCT, crossover Sponsorship: Thompson Medical Co., Inc. and the MinnesotaAgricultural Experiment Station USA Duration of symptom recording:	Data source: 20 "healthy" American lactose maldigesters adults based soley on breath hydrogen test. Inclusion criteria: Breath hydrogen concentration to >20 ppm (>1.80 x 10^{-6} g H_2/liter air) after ingestion of 400 ml of low-fat (2%) milk	Age range: 25-40 Gender: women 50%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	400 ml of low-fat (2%) milk (lactose content 20 g) plus β-galactosidase (β-gal) enzyme preparations 1) Lactogest soft gel capsules x 2 (Thompson Medical Inc, New York, NY), 2) Lactogest	400 ml of low-fat (2%) (lactose content 20 g) plus two soft gel vitamin E capsules containing 420 rag/capsule of α-tocopherol in soybean oil as a Placebo (Pharmacaps Inc,	The difference in symptom scores (from baseline), based on the summation of observed symptoms from the scoring charts (on a 0 = none to 5 = severe scale) of the 20 subjects. Conclusion(s): Symptoms were	Allocation concealment: adequate (small brown coded envelopes) Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
8 hours	containing approximately 20 g of lactose. Exclusion criteria: Pregnant or lactating, had prior gastrointestinal surgery, had illness that would interfere with the experiment, or had used antibiotics within the past 30 days. Methods to measure outcomes: Subjects kept a dairy of symptoms and self-rated gas, stomach pain and/or cramps and diarrhea and/or loose stool for each hour from 0 to 8 hours following the test meal. Scores are expressed as the mean of the sum of scores rating symptoms from 0 (none) to 5 (severe) for each hour from baseline to 8 hr after the challenge.		capsules x 4 3) Lactaid caplets x 2 (Lactaid Inc, Pleasantville, New Jersey) or 4) DairyEase chewable tablets x 2 (Glenbrook Laboratories, New York, NY)	Elizabeth, New Jersey)	significantly less severe with all the β-galactosidase products.	described: no withdrawals reported
Brand, 1991[72] RCT, crossover Sponsorship: Not reported Australia Duration of symptom recording: 4 hours	Data source: Six healthy adult Australian subjects with lactose malabsorption. Subjects were not noted to be symptomatic at baseline. Inclusion criteria: Diagnosis of lactose malabsorption was	Mean age (range): 33 (29 to 44) Gender: female 83%. Ethnicity: The 6 subjects were immigrants from Indonesia, Japan, Malaysia, and Laos.	300 mL 50% lactose reduced milk (Lacto Lo) (lactose content 2.4 g) 300 mL 80% lactose reduced milk (Cotee) (lactose content 1 g)	300 mL whole milk (lactose content 4.8 g), tested twice in each individual *(n* = 12). After an overnight fast the subjects consumed 300 mL of each of five milk products in a	Number of subjects who reported specific symptoms. Conclusion(s): The results suggest that a 50% level of lactose reduction in milk may be adequate to relieve the signs and symptoms of milk	Allocation concealment: unclear Blinding: single Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	based on the results of a challenge with 300 mL whole milk contain-ing 14 g lactose after an overnight fast based on a peak breath hydrogen excretion >20 ppm. Methods to measure outcomes: At hourly intervals they rated their symptoms (cramps, flatulence, and diarrhea) on a scale of 0, no symptoms; 1, mild; 2, moderate; and 3, severe.	Comorbidities: not reported Cointerventions: not reported	300 mL 80% lactose reduced milk (Balance) (lactose content 1 g) 300 mL 95% lactose reduced milk (Digestelact) (lactose content <0.25 g)	single-blind fashion and random order on separate occasions 3-5 d apart.	intolerance in the majority of healthy adults with lactose malabsorption.	withdrawals reported
Cavalli-Sforza, 1986[73] RCT, crossover Sponsorship: Parmalat Spa Italy Duration of symptom recording: 1 day	Data source: 80 Italian adults, data from 71 subjects: 40 lactose malabsorbers and 30 lactose absorbers. Inclusion criteria: Adults free from gastrointestinal diseases and diabetes. All subjects were give lactose tolerance test (50 g lactose in 200 mL water). Subjects were defined as lactose malabsorber if maximum increase in blood glucose concentration above fasting level was <20 mg/dL. Methods to measure outcomes:	*All subjects (N=80)* Mean age (range): 34 (18 to 69) Gender: female 66% Ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	Regular whole hydrolyzed milk (lactose content 0.5 g/dL) and fat content of 3.2 g. Regular skim hydrolyzed milk (lactose content 0.65 g/dL and fat content of 0.10 g.) Each type of milk was taken on 4 consecutive days in Increasing quantities: 125, 250, 500, 1000 mL. The larger quantities could be divided into 2 to 6 intakes during the day.	Regular whole milk (lactose content 4.9 g/dL) and fat content of 3.3 g. Regular skim milk (lactose content 5.10 g/dL and fat content of 0.15 g; 12.75 per milk serving)	Symptom response to the intake of the 4 milk types, percent of cases. Conclusion(s): Lactose malabsorbers had significantly fewer symptoms with skim milk vs. whole milk. The authors found, contrary to earlier findings, that fat seemed to contribute to milk intolerance in lactose malabsorbers rather than reduce it.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: no, 74 of 80 completed study satisfactorily but data only for 71 (3 refused to drink milk at room temperature) Study withdrawals adequately described: yes

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	Questionnaire was given to subjects to indicate whether they experienced diarrhea, flatulence, bloating, or abdominal pain during the 24 hours after consuming the milk test. Symptoms were rated mild = 1, moderate = 2 or severe = 3 in intensity. A total for the 4 symptoms could range from 0 to 12.					
Rosado, 1984[74] RCT Sponsorship: Limited, industries provided the enzymes (SugarLo Co. (Pleasantville, NJ) and G.B. Fermentation (Kingstree, SC)) USA/Mexico Duration of symptom recording: 1 day	Data source: 50 Mexican adults were enrolled, 25 lactose malabsorbers and 25 absorbers. Inclusion criteria: No inclusion criteria, subjects unselected. Methods to measure outcomes: Subjects completed symptom questionnaire document presence or absence of 4 gastrointestinal symptoms (abdominal cramps, gas/flatulence, vomiting, and/or diarrhea). Absence of all 4 symptoms = lactose tolerance. 0 =absent; 1=mild; 2=moderate; 3=severe, except for diarrhea which was always marked a 3.	Age range: 19-53 Gender: women 64%. Race/ethnicity: Mostly Mexican with various degrees of European and Indian descent. Comorbidities: NR Cointerventions: NR	1) LactAid 1g combined with 360 mL milk, reconstituted from powdered whole milk (lactose content 18 g) 2) 360 mL pre-hydrolyzed milk. A minimum of 72 hours between tests.	360 mL milk, reconstituted from powdered whole milk (lactose content 18 g)	Number of subjects reporting symptoms (minor or major). Conclusion(s): Addition of LactAid significantly reduced symptoms of intolerance among the 25 lactose malabsorbers subjects.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported Funding: industry supplied supplies

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	Total points were then summed for each of the treatment periods. A score ≥4 = major symptomaology, ≤3 = minor. Exclusion criteria: recent history or concurrent use of antibiotics or recent gastrointestinal disease.					
Haverberg, 1980[75] RCT, crossover Sponsorship: National Dairy Council USA Duration of symptom recording: 1 day	Data source: 67 American lactose malabsorbing (determined by blood glucose analysis) and 43 lactose absorbing adolescent volunteers. Classification was based on biochemical vs. subjective symptomatic response to lactose. Methods to measure outcomes: Subjects reported abdominal symptoms on a questionnaire containing yes/no or multiple choice questions regarding symptoms over 24 hours after consumption. Occurrence of diarrhea, ≥ 2 mild GI symptoms or ≥ 1 moderate or severe symptom was noted as a positive response of intolerance to the test drink.	Age range: 14-19 Gender: not reported Race/ethnicity: black 53%, white 40%; Latin American 7%. Comorbidities: not reported Cointerventions: not reported	240 or 480 mL lactose-free chocolate dairy drink.	240 or 480 mL lactose-containing (lactose content 10.8-21.6 g) chocolate dairy drink.	Number of subjects reporting symptoms during 24 hours after consumption 18% of lactose malabsorbers were symptomatic after consuming 240 mL of lactose-free solution versus 28% after consuming 240 mL lactose solution. Conclusion(s): Results indicate that most of the individuals who reported GI symptoms after consuming the beverages did so due to other reasons besides the lactose content.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses:100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
Kwon, 1980[76] RCT, crossover Sponsorship: National Dairy Council USA Duration of symptom recording: 1 day	Data source: 45 American lactose malabsorbing (determined by blood glucose analysis) and 42 lactose absorbing adolescent volunteers. Classification was based on biochemical vs. subjective symptomatic response to lactose. Methods to measure outcomes: Subjects reported abdominal symptoms on a questionnaire containing yes/no or multiple choice questions regarding symptoms (bloating, flatulence, cramps, or diarrhea) over 24 hoursafter consumption by checking 1=none; 2= mild; 3=moderate; and 4=severe. Presence of ≥1 symptom was considered as a positive intolerant response.	*All subjects (N=87)* Age range: (14-19) Gender: not reported Race/ethnicity: black 30%, white 64%; Asian 6%. Comorbidities: not reported Cointerventions: not reported	240 or 480 mL lactose-free chocolate dairy drink.	240 or 480 mL lactose-containing (lactose content 10.8 or 21.6 g) chocolate dairy drink.	Number of subjects reporting symptoms during 24 hours after consumption Among lactose malabsorbers, 27% were symptomatic after consuming 240 mL of lactose-free solution versus 9% after consuming 240 mL lactose solution. Conclusion(s): Factors other than lactose malabsorption may be responsible for a significant proportion of mild symptoms of “milk intolerance” in an adolescent population similar to this study.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Rorick, 1979[77] RCT, crossover Sponsorship: National Dairy Council USA Duration of symptom recording: 1 day	Data source: 87 American elderly volunteers, in which 23 were lactose malabsorbers (determined by breath hydrogen analysis after ingestion of 25 g lactose) and 64 lactose absorbers.	*All subjects (N=87)* Mean age (range): 77 (60-97). Gender: women 77% Race/ethnicity: Northern/western European ancestry 76% (35% of the malabsorbers),	240 mL lactose-free chocolate dairy drink.	240 mL lactose-containing (lactose content 10.8 g) chocolate dairy drink.	Number of subjects reporting intolerance to test drinks based on GI symptoms during the afternoon after consumption. Symptom frequency was not significantly different between beverages in both	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	Inclusion criteria: Subjects with no known gastrointestinal disease. Methods to measure outcomes: Subjects were interviewed the following morning after the test and were asked to state the occurrence severity of gas, bloating, cramps, or diarrhea during the previous afternoon. Symptom severity was based as follows: none; mild (noticeable, but not troublesome); moderate (troublesome, but not seriously uncomfortable); severe (uncomfortable, could not carry out normal activities).	Jewish 11% (30%), black 8% (22%), Southern Italian 5% (13%). Comorbidities: not reported Cointerventions: not reported			malabsorbers and absorbers. Conclusion(s): Authors conclude factors other than lactose malabsorption appeared to be responsible for the symptoms of intolerance reported and most may have been psychosomatic in origin.	withdrawals reported
Lisker, 1978[78] RCT, crossover Sponsorship: Programa Nacional de Alimentos of the Consejo Nacional de Ciencia Y Tecnología de México. Mexico Duration of symptom recording: 6 hours	Data source: 150 Mexican volunteers, in which 97 were lactose malabsorbers (determined by blood glucose analysis [<25 mg/dl considered deficient lactase activity] after ingestion of 50 g lactose). Inclusion criteria: Subjects with no known gastrointestinal disease, diabetes. Methods to measure	*All subjects (N=150)* Mean age (range): 24 (16-50). Gender: women 41% Race/ethnicity: Mexican 100% 60 of the volunteers had previously participated in lactose mal-absorption studies and were also	250 mL lactose-free milk plus 7.1 glucose. Powdered chocolate added to mask flavors.	250 mL regular milk (lactose content 12.5 g). 250 mL regular milk plus additional 25 g lactose added (lactose content 37.5 g).	Conclusion: Authors concluded that lactose-intolerant subjects are indeed lactose-intolerant and that the frequency of abdominal symptoms that occur in persons with lactose malabsorption increases directly with the lactose content in milk.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	outcomes: Symptoms were rated according: 1+ if mild; 2+ if moderate; 3+ if marked. Symptoms were scored as severe if diarrhea was present or if a cumulative rating of other symptoms (abdominal cramps, bloating, flatulence) was 4+. Cumulative rating less than 4+ was considered mild.	aware they could tolerate at least 250 mL of milk at one time without difficulty. Comorbidities: not reported Cointerventions: not reported				
Paige, 1975[79] RCT, crossover Sponsorship: Maternal and Child Health Services and National Institutes of Health USA Duration of symptom recording: 90 minutes	Data source: 22 lactose-malabsorbers and 10 lactose absorber African American volunteers. Malabsorption was based on blood sugar rise of 26 mg/mL following ingestion of lactose load (50 g/ m^2 of body surface) Inclusion criteria: no overt gastrointestinal or metabolic disease, Methods to measure outcomes: Symptoms voluntarily mentioned were recorded. Subjects were not specifically asked if they developed any symptoms commonly associated with lactose intolerance.	*All subjects (N=32)* Age range: 13-19. Gender: not reported Race: black 100%. Comorbidities: not reported Cointerventions: not reported	240 mL whole milk, 90% hydrolyzed (lactose content 1.2 g) by adding lactase from *Saccharomyces lactis* 240 mL.whole milk, 50% hydrolyzed (lactose content 6 g) by adding lactase from *Saccharomyces lactis*.	240 mL whole milk (lactose content 12 g).	Number of subjects reporting symptoms during 90 minutes after consumption. 90% hydrolyzed milk (n=22): 3 including 2 from the whole milk group) 90% hydrolyzed milk (n=18): none Whole milk (n=22): 3 Conclusion(s): Authors concluded hydrolyzed milk may serve as alternative to milk in subjects with low lactase levels.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Jones 1976, Study 1[71] Single blind RCT no	Data Source: 16 American adult volunteers	Mean age 25 (range 23-55) Gender: women	1. 50% lactose reduced skim milk 591 ml (30 g	Regular skim milk 591 ml (50 g lactose	Sum of score of bloating, gas, cramps and diarrhea on scale:	Allocation concealment: unclear

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
masking to taste, crossover USA Duration:8 hours Funded by National Dairy Council and NY State Agriculture Experiment station hatch project Hypothesis: 1. milk with lower lactose better tolerated than regular milk, 2. compare symptoms after whole, skim milk, and lactose solutions	Inclusion criteria: LI on basis of rise in blood glucose of less than 25 mg/100mL after 50 g lactose injection Methods to measure outcome: Asked about any symptoms of bloating, gas, abdominal cramps and diarrhea on 0-3 point scale, summed	31% Race/ethnicity: Asian 25%; black 19%; Latin-American 13%; other 44% Comorbid: none Co-intervention: none	lactose) 2. 75% lactose reduced skim milk 591 ml (15 g lactose)		0-none, 1=mild, 2= moderate, 3=severe. Conclusion(s): 1) Lower lactose milk better tolerated; 2.) Whether milks were given with or without food had no significant effect on symptoms	Blinding: single no masking Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
B. Prebiotics or probiotics **I. Studies where subjects were reported to be symptomatic at baseline in addition to LI testing**						
Newcomer, 1983[80] RCT, crossover Funding: US national diary council and NC State University Dairy Foundation USA Duration: 10 weeks Hypothesis: Unfermented acidophilus milk is better tolerated than regular milk	Data source: 28 US volunteers Inclusion criteria: No symptoms and negative hydrogen breath test for controls and symptoms and positive hydrogen breath test for cases (defined as H2 excretion of .30 ml/min after 50gm lactose plus symptoms) Methods to measure outcomes: Subjects kept a diary for scoring 0-4; 0=no trouble, 1=slight symptoms, 2=mild s/s, 3=	Range age: 18-69 Gender: NR Race: NR Comorbid: 5/18 cases also had IBS Co-intervention: none	Unfermented acidophilus milk: 2% milk with L. acidophilus added for approx 7x10(6) colony/ml (one 8 oz glass with three meals, 3x/day for total of 720 ml/day)	2% milk: 3 8 oz glasses per day, one with each meal for total of 720 ml/day	Median of cumulative s/s score over 10 weeks as sum of diarrhea+pain+gas+ borborygmi over 5 2-week periods for LI group Conclusion(s): No difference in tolerance of regular milk vs. unfermented acidophilus milk	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	moderate, 4= severe) for 4-10 weeks Loss to followup: none					
II. Studies where subjects did not have symptoms of LI at baseline or not reported and only underwent breath/other testing						
Lin, 1998[81] RCT, crossover Sponsorship: National Science Council ofTaiwan Taiwan Duration of symptom recording: 8 hours	Data source: 20 Taiwanese subjects. Inclusion criteria: Maldigesters were classified on the basis of a rise in breath hydrogen concentration of >20 ppm after ingestion of 400 ml of milk containing approxi-mately 20 g of lactose. Methods to measure outcomes: Subjects rated symptoms on a 0-5 (none to severe) scale for each hour from hour 1 to hour 8 following each of the diets.	No information on age and gender provided. Comorbidities: not reported Cointerventions: not reported	1) 400 ml of 2% low-fat milk containing *L. acidophilus* at a cell concentration of 108 CFU/ml; 2) 400 ml of 2% low-fat milk containing *L. acidophilus* at 109 CFU/ml; 3) 400 ml of 2% low-fat milk containing *L. bulgaricus* at 108 CFU/ml; 4) 400 ml of 2% low-fat milk containing *L. bulgaricus* at 109 CFU/ml. All milk products were non-fermented.	400 ml of 2% low-fat milk	Symptom scores are expressed as the mean of the sum of stomach pain, gas, and diarrhea scores rated from 0 to 5 (none to severe) for each hour from 0 to 8 hr after consumption of the diets. Conclusion(s): Non-fermented milks containing *L. bulgaricus* 449 at 10^8 and 10^9 CFU/ml were effective in reducing symptoms.	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Mustapha, 1997[82] RCT, crossover Sponsorship: Minnesota-South Dakota Diary Foods Research Center United States Duration of symptom recording:	Data source: 11 lactose maldigesting American subjects Inclusion criteria: Maldigesters were classified on the basis of a rise in breath hydrogen concentration of >20 ppm after	Age range: 25-42 Gender: women 55%. Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	1) 400 mL *L. acidophilus* 4356 (b-galactosidase (b-gal) activity 1.22; lactose content 15-16 g). 2) 400 mL *L. acidophilus* B (b-gal) activity 0.81;	400 mL low fat milk (b-gal activity 0; lactose content 15 g)	Mean symptom response 0-5 (none to severe), summed from hour 1 to hour 8. Conclusion(s): Acidophilus milk containing *L. acidophilus* N1 was the most effective of	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
8 hours	ingestion of 400 ml of milk containing approxi-mately 18 g of lactose. None had any GI illness or had taken antibiotics in the prior three months of the study. Methods to measure outcomes: Subjects rated symptoms on a 0-5 (none to severe) scale for each hour from hour 1 to hour 8 following each of the diets. Diarrhea was monitored 24 hours after diet.		lactose content 15-16 g). 3) 400 mL *L. acidophilus* N1 (lowest b-gal activity 0.50; lactose content 15-16 g). 4) 400 mL *L. acidophilus* E (b-gal) activity 0.79; lactose content 15-16 g).		the four strains in improving lactose digestion and tolerance.	described: no withdrawals reported
Jiang, 1996[83] RCT, crossover Sponsorship: Minnesota Agricultural Experiment Station USA Duration of symptom recording: 1 day with 3 days in b/w Hypothesis: HB after ingestion of milk with different strains of B. longum	Data source: 15 American volunteers Inclusion criteria: lactose maldigesters on basis of rise of >20ppm after ingestion of 400 ml of milk (16 gm lactose) on hydrogen breath test using Levitt/Donaldson method. Methods to measure outcomes: ranked scale of symptoms for abdominal pain, flatulence, borborygmi, diarrhea and meteoism: 0=none, 1=slight, 2=mild, 3=moderate, 4=moderately severe, 5= severe summed for hours 1-8. flatus frequency: mean num of	Age range: 24-42, mean 29.7 Gender: women 8(52%). Race: white 100% Comorbidities: no GI disorders Cointerventions: not reported	3 test meals: 1) 400 ml 2% milk with *Bifidobacterium longum* B6 from m-MRS broth containing lactose 2) 400 ml 2% milk with *B. longum* B6 from Sanofi biomed as a concentrated frozen culture 3) 400 ml of bifidus milk with *B. longum* ATCC 15708 from m-MRS broth containing lactose	One meal 400 ml of 2% milk	Mean symptom response 0-5 (none to severe), summed from hour 1 to hour 8. Conclusion(s): Consumption of milk containing B6 grown with lactose resulted in significantly less flatulence vs. milk or the milk containing B6 grown with both lactose and glucose. Authors concluded that milks containing *B. longum* might reduce symptoms from lactose malabsorption when the culture is grown in a medium containing only lactose to induce	Allocation concealment: yes Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	gas passages over 8 hours, plus hydrogen breath test mean reading over 8 hours				a higher *β*-galactosidase level and increase rate of lactose uptake.	
Vesa, 1996[84] RCT crossover France Funding: Yoplait Sodima, France Duration of symptom recording: 8 hours Hypothesis: Addition of *L. bulgaricus* to increase lactase activity may make milk easier to tolerate compared to yogurt and milk with *L. acidohpilus* and bifidobacterium	Data source: 15 Healthy French volunteers (reported 14) Inclusion criteria: lactase deficient by hydrogen breath test Methods to measure outcomes: symptom score 0-4 (0=no symptoms, 1=mild, 2=moderate, 3= fairly strong, 4=very strong symptoms) for abdominal bloating, flatulence, abdominal pain and loose stool compared mean+/-SE and sum of symptoms	Age range: 20-45 Gender: women 11 (73%) Race: 100% Caucasian Comorbidities: none Cointerventions: not reported	3 fermented dairy products each with 18gm lactose in 250 ml water: 1) Ofilus (Yoplait, France; has *L. acidophilus* and bifidobacterium) 320 ml 2) Bulgofilus (ofilus bacteria+ *L. bulgaricus*) 400 ml 3) Yoplait yogurt 500 ml	Lactulose 10gm in 250 ml water	Conclusion(s): Significantly less bloating with bulgofilus compared to lactulose and sum score less with bulgofilus compared to lactulose	Allocation concealment: unclear Blinding: unclear if double Intent-to-treat analyses: no 15 enrolled, 14 reported Study withdrawals adequately described: 1 withdrawal reported Industry funding
Lerebours, 1989[85] RCT, parallel study Sponsorship: none reported. France Duration of symptom recording: unclear	Data source: 16 healthy subjects born in Cameroon. Inclusion criteria: lactose intolerance on the basis of an increase in breath hydrogen concentration >20 ppm after ingestion of 440 mL milk containing 18 g lactose. Only two subjects experienced mild flatulence after milk ingestion. Methods to measure outcomes; No methods	Age range: 20-53 Gender: NR Race: black 100%. Comorbidities: not reported Cointerventions: not reported	125 g yogurt (n=8) three times daily (breakfast, bunch, and dinner) (lactose content 18 g/d) Meals were given over 8 consecutive days.	125 g fermented-then-pasteurized milk (FPM) (n=8) without living acid bacteria times daily (breakfast, bunch, and dinner) (lactose content 18 g/d)	Presence or absence of symptoms. Conclusion(s): Although lactose malabsorption was higher with FPM than with yogurt, the subjects reported no gastrointestinal distress after consuming 1PM for 8 days but it must be stressed that only two subjects experienced mild symptoms after milk ingestion. These	Allocation concealment: unclear Blinding: double Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	reported.				data indicate that besides lactose digestion, other factors are involved in inducing or preventing gastrointestinal distress during the consumption of dairy products by lactase-deficient subjects.	
Martini, 1987[86] RCT crossover Sponsorship: The National Dairy Board In cooperation with the National Dairy Council USA Duration of symptom recording:8 hours	Data source: 16 American healthy subjects. Inclusion criteria: lactose intolerance on the basis of an increase in breath hydrogen concentration >20 ppm after ingestion of milk containing 20 g lactose. Methods to measure outcomes; intolerance symptoms were recorded by the subjects.	Age range: 18-26 Gender: male 100% Race: NR Comorbidities: not reported Cointerventions: not reported	A. Flavored products (n=9) 1) 465 g strawberry flavored yogurt (lactose content 20 g) 2) 410 g ice milk (lactose content 20 g) 3) 400 g ice cream (lactose content 20g) B. unflavored products (n=8) 1) 455 g unflavored yogurt (lactose content 20 g) 2) 410 g unflavored yogurt FY-1 (lactose content 20 g) 3) 410 g unflavored yogurt FY-2 (lactose content 20 g) 4) 410 g unflavored yogurt FY-3 (lactose content 20 g) One subject received both products.	415 g whole milk (lactose content 20 g)	Subjects reporting symptoms of gastrointestinal distress. Conclusion(s): Subjects were free of symptoms after consuming flavored and unflavored yogurts. Tolerance to frozen yogurt same as for ice cream and ice milk.	Allocation concealment: unclear Blinding: single-blind (subjects were not informed of the identity of each product but no attempt to mask flavors was undertaken) Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
Savaiano, 1984[87] RCT crossover, single blind (no attempt to mask flavor or texture) USA University of MN Agricultural Experiment Station, VA, NIH Duration of s/s recording: 8 hours Hypothesis: yogurt produces less symptoms than other milk products	Data source: 9 American healthy subjects. Inclusion criteria: lactose intolerance on the basis of an increase in breath hydrogen concentration >20 ppm after ingestion of milk containing 20 g lactose. Methods to measure outcomes; intolerance symptoms were recorded by the subjects, scale not reported. Symptoms reported were diarrhea, flatulence, abdominal pain	Age range: 20-28 Gender: NR Race: NR Comorbidities: not reported Cointerventions: not reported	1) 500 gm yogurt 2) 420 gm sweet acidophilus milk 3) 465 gm cultured milk (buttermilk) 4) 500 gm pasteurized yogurt	410 gm milk	No symptoms reported when yogurt or pasteurized yogurt was fed. 4 and 5 of the nine reported symptoms with milk and sweet acidophilus milk respectively. Conclusion(s): Yogurt is unique due to ability to enhance lactose digestion	Allocation concealment: unclear Blinding: single (no attempt to mask flavor or texture) Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
C. Modifications to diet or other therapies						
Cappello, 200[88] RCT Sponsorship: not reported Italy Duration of symptom recording: 40 days	40 symptomatic Italian subjects with positive breath H2 test for lactose intolerance Methods to measure outcomes: Subjects filled in a questionnaire related to the intensity of symptoms (bloating, abdominal pain, flatulence and diarrhea). Symptoms score referred to the 5 days preceding each evaluation and scored as: 0=absent; 1=mild (awareness of a	Mean age: 44 Gender: women 80%. Race: Not reported Comorbidities: not reported Cointerventions: not reported	1) Rifaximin 800 mg/day x 10 days (n=14) 2) No-milk diet x 40 days (n=13)	Placebo (n=5) x 10 days	Intensity of symptoms at baseline, 10d and 40 d (mean ± SD). Conclusion(s): The total symptom score significantly improved after rifaximin and lactose-free diet.	Allocation concealment: unclear Blinding: partially open. blinding of rifaximin and placebo not reported Intent-to-treat analyses: no Study withdrawals adequately described: no Funding: not reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	symptom but easily tolerated); 2=moderate; 3=severe; and 4=very severe.					
D. Colonic adaptation studies						
Hertzler, 1996[89] RCT, crossover Sponsorship: The National Dairy Board In cooperation with the National Dairy Council USA Duration of symptom recording: 10 days	Data source: 20 American lactose maldigesting subjects. Inclusion criteria: Healthy nonsmokers who had not used antibiotics in the preceding 2 months and reported no history of functional bowel complaints. Subjects were classified as lactose maldigesters based on a rise in breath hydrogen of >20 ppm (0.9 ımol hydrogen/L air) after a challenge dose of lactose (0.7 g/kg body wt) administered after an overnight fast. Methods to measure outcomes: Subjects rated symptoms hourly during the breath hydrogen tests using a ranked scale: 0=none, 1=slight, 2=mild, 3=moderate, 4= moderately severe, 5= severe. Data are reported as the sum of	Mean age: 30 Gender: women 25%. Race: Asian 70%, black, Latin-American, and white 10% each Comorbidities: not reported Cointerventions: not reported	Dextrose for days 1-10 and crossed over to the other feeding period for days 12-21. Initial dosage was 0.6 g • kg body wt^{-1} • d^{-1}, which was increased by 0.2-g/kg increments every other day up to a maximum of 1.0 g • kg^{-1} • d^{-1}. On days 11 and 22 an aqueous lactose challenge (0.35 g/kg) was administered after an overnight (>12 hours) fast. Breath hydrogen excretion and intolerance symptoms were monitored hourly for 8 hours after the challenge dose was consumed	Lactose for days 1-10 and crossed over to the other feeding period for days 12-21. Initial dosage was 0.6 g • kg body wt^{-1} • d^{-1}, which was increased by 0.2-g/kg increments every other day up to a maximum of 1.0 g • kg^{-1} • d^{-1}. On days 11 and 22 an aqueous lactose challenge (0.35 g/kg) was administered after an overnight (>12 hours) fast. Breath hydrogen excretion and intolerance symptoms were monitored hourly for 8 hours after the challenge dose was consumed.	Symptoms rating after lactose (L) or dextrose (D) feeding periods (mean ± SEM). The maximum possible score for any individual symptom would be 40 (a *"5"* rating each hour for 8 hours). Conclusion(s): Authors concluded that there is colonic adaptation to regular lactose ingestion and this adaptation reduces lactose intolerance symptoms.	Allocation concealment: unclear Blinding: noted as blinded, unclear if double-blinded Intent-to-treat analyses: no Study withdrawals adequately described: no

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	hours 1-8. During the feeding periods, subjects recorded symptoms once per day each evening during the feeding periods using the same scale mentioned above.					
E. Incremental lactose loads or studies examining different levels of lactose						
Hertzler, 1996[90] RCT, crossover Sponsorship: Minnesota Agricultural Experiment Station USA Duration of symptom recording: 1 day	Data source: 13 American lactose maldigesting subjects. Inclusion criteria: Subjects were classified as lactose maldigesters based on a rise in breath hydrogen of >20 ppm (0.9 ımol hydrogen/L air) during a challenge dose of lactose (20 g) after a 12 hours fast. Methods to measure outcomes: Subjects rated symptoms of flatulence, abdominal pain, and diarrhea hours 1 through 8 following challenge dose. A ranked scale was used; 0=none, 1=slight, 2=mild, 3=moderate, 4= moderately severe, 5= severe.	Mean age: 32 (range 21 to 42) Gender: women 46%. Race: NR Comorbidities: not reported Cointerventions: not reported	Five treatment solutions consisting of lactose dissolved in 240 mL of tap water. 1) Lactose 0 g 2) Lactose 2 g 3) Lactose 6 g 4) Lactose 12 g 5) Lactose 20 g		Symptoms rating after each challenge dose (mean ± SEM). The maximum possible score for any individual symptom would be 40 (a *"5"* rating each hour for 8 hours). Conclusion(s): Lactose maldigesters may be able to tolerate foods with ≤6 g lactose per serving such as hard cheeses and small servings (≤120 mL) of milk.	Allocation concealment: unclear Blinding: double-blinded Intent-to-treat analyses: no Study withdrawals adequately described: no
Newcomer, 1978[91] RCT, crossover Sponsorship:	Data source: 59 lactase deficient American Indians.	Mean age (range): 18.7 (5-62). 44 were <18 years of	6 breakfasts randomly distributed. Sugar		Number of subjects with symptoms.	Allocation concealment: unclear

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
National Institutes of Health and United States Public Health Service. USA Duration of symptom recording: 8 hours	Inclusion criteria: lactase deficiency determined by breath hydrogen concentration to >20 mL/min after ingestion of 50 g (less for children) of lactose. Methods to measure outcomes: A subject was considered to have a positive symptomatic response if he/she had ≥1 loose stools or had a grade 2+ or higher in at least one of the following symptoms: abdominal cramps/pain, bloating or gas, borborygmi, flatulence. Symptoms were rated according: 0 = no trouble; 1+ = slight; 2+ = mild; 3+ = moderate, subject would normally avoid a breakfast causing these symptoms; 4+ = severe, subject would be unable to carry on usual activities.	age. Gender: women 47% Race/ethnicity: American Indian 100%	packets with lactose ranging from 0 to 18 g added to 8 ounces of Ensure drink. Breakfast 1: 0 g lactose + 18 g glucose plus galactose (G+G). Breakfast 2: 3 g lactose + 15 g G+G. Breakfast 3: 6 g lactose + 12 g G+G. Breakfast 4: 9 g lactose + 9 g G+G. Breakfast 5: 12 g lactose + 6 g G+G. Breakfast 6: 18 g lactose + 0 g G+G.		Conclusion(s): A modest amount of lactose (1-1½ glasses of milk), when consumed with a meal, was well tolerated by lactase-deficient American Indians.	Blinding: double, symptoms assessed by "blinded observer" Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported
Stephenson, 1974[92] Un-blinded RCT, attempt made to mask to taste, crossover USA Duration:8 hours Funded by National	Data Source: n=35 U.S. adults, with and without LI on basis of rise in blood glucose of less than 20 mg/100mL after 50 g lactose ingestion Methods to measure outcome: Asked about	Median age 25 (23-55 range) Gender: women 54% Race/ethnicity: white 71%, non-white 29% Co-morbid: none	Day 1, all 35 got 50 gm lactose. Those with symptoms got 15, 30, 50 gm lactose in water or milk serially. Those with no symptoms got 100, 150 and	Placebo 250 ml (saccharin, lemon juice water)	Sum of score of bloating, gas, cramps and diarrhea on scale: 0=none, 1=mild, 2= moderate, 3=severe. Conclusion(s): Most adults with lactose	Allocation concealment: unclear Blinding: single no masking Intent-to-treat analyses: one person lost to

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
Dairy Council and NY State Agriculture Experiment Station hatch project Hypothesis: Higher doses of lactose poorly tolerated	any symptoms of bloating, gas, abdominal cramps and diarrhea on scale of mild moderate and severe, summed	Co-intervention: none	200 gm lactose in water and milk serially		intolerance can tolerate up to 30 gm lactose	followup Study withdrawals adequately described: yes, one withdrawal reported, data missing on up to 3 individuals in different groups
F. Studies with irritable bowel syndrome subjects						
Parker, 2001[93] RCT, crossover Sponsorship: NR UK Duration of symptom recording: 1 week	Data source: 122 British IBS patients were referred for a lactose hydrogen breath test. The breath test was positive in 33 (27%) and negative in 89 (73%). Subjects in the positive group were then placed on a low lactose diet for 3 weeks. The daily intake of lactose from this diet was <1 g. Patients improving on the low lactose diet were given double-blind, placebo-controlled challenges to confirm lactose intolerance. Methods to measure outcomes: Symptom score was based on eight variables: abdominal pain, daily bowel movements, urgency to defecate, consistency of feces,	*Data for the 33 subjects with positive hydrogen breath test*. Mean age NR. Age <50 years 73%; Gender: women 76% Race/ethnicity White 85% (n=28), Asian 9% (n=3), Middle-Eastern 6% (n=2), Comorbidities: not reported Cointerventions: not reported	Three active tests were given in random order for 7 of 9 subjects improving on low-lactose diet: lactose 5 g, 10 g, or 15 g, and placebo mixed with 285 ml water and taken at breakfast on 2 consecutive days with 5 days' rest between each test. Symptoms scores were completed daily for test and rest days. Subjects remained on low lactose diet during double-blind, placebo-controlled test period.		Conclusion(s): During double-blind phase, 2/7 subjects (29%) developed increasing symptoms with increasing doses of lactose. Although 5 of the 7 were affected by 15 g lactose, 5 subjects had worse symptoms with 5 g than 10 g, suggesting that many LM patients can tolerate up to 12 g per day. Patients with lactose intolerance were not distinguishable from others with IBS on the basis of symptoms, and treatment with a low lactose diet gave disappointing results.	Allocation concealment: unclear Blinding: double-blinded Intent-to-treat analyses: 100% followup although 2 subjects meeting eligibility did not participate for unknown reasons Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	flatulence, headache, abdominal distension, and general well-being. Each symptom was scored from 0 to 4, 0 being no symptoms and 4 most severe. Urgency was scored from 0 to 3. The maximum cumulative score = 31.					
Böhmer 1996[94] Sponsorship: not reported The Netherlands Duration of symptom recording: 6 weeks	Data source: 105 Caucasian Dutch subjects, 70 with IBS and 35 healthy controls Inclusion criteria: Subjects were screened for lactose mal-absorption (LM) and were not aware of the test results. Diagnosis of IBS after exclusion of organic causes. Subjects had to fulfill at least two criteria: visible abdominal distension; pain relief with defecation; more frequent stools at pain onset; looser stools at pain onset; passage of rectal mucus; and feeling of incomplete evacuation. Subjects were classified as lactose malabsorbers based on a rise in breath hydrogen of >20 ppm above basal level	*IBS subjects* (n=70 of which 17 had LM) Median age (range): 35.7 years (18 to 59) Gender: women 74% Race/ethnicity: white 100% *Healthy control subjects* (n=35) Median age (range): 33 years (21 to 51) Gender: women 74% Race/ethnicity: white 100%	Lactose restricted diet		Cumulative symptom scores at 3 and 6 weeks, comparing IBS subjects with LM vs. IBS subjects without LM. Conclusion(s): the mean symptom score of the IBS with LM showed a statistically significant decrease after 6 weeks of a lactose restricted diet.	Allocation concealment: unclear Blinding: double-blinded Intent-to-treat analyses: no dropouts reported Study withdrawals adequately described: none

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	during a challenge dose of lactose (50 g) after a 12 hours fast. Methods to measure outcomes: subjects scored symptoms (pain, flatulence, distension, diarrhea, mucus, incomplete evacuation) 0=no complaints, 1=mild; 2=moderate; and 3 as severe. A maximum cumulative score = 18.					
Lisker 1989[95] RCT, crossover Sponsorship: Mr. A. Kligerman, President of Sugar Lo/Lact Aid company (lactase and placebo vials) Mexico Duration of symptom recording: months: 3 months	Data source: 12 Mexican subjects with IBS whose diets regularly included milk. Eight of the subjects were lactose mal-digesters (when challenged with 12.5 lactose and diagnosed by hydrogen breath test ≥ 20 ppm). Inclusion criteria: 1) diagnosis of IBS based on chronic abdominal pain, altered bowel habits, and absence of organic disease; 2) regular diet included consumption of milk/dairy products ≥8 oz. glass of milk daily or equivalent lactose intake; 3) patients lived close enough to center	Mean age (range): 49 years (24 to 72) Gender: women 75% Race/ethnicity: not reported Comorbidities: not reported Cointerventions: not reported	Treatment A group Lactase x 4 weeks, then placebo x 4 weeks, then lactase x 4 weeks. Prior to 3 month study phase there was a 1 month non-intervention, control period. Lactase (derived from *Kluyveromyces lactis*) was used *in vitro* (added in entirety to liter of milk the day before consumption) and *in vivo* (added at mealtime when consuming lactose-containing foods away from home)	Treatment B group Placebo x 4 weeks, then lactase x 4 weeks, then lactase x 4 weeks. Prior to 3 month study phase there was a 1 month non-intervention, control period.	Symptoms noted as better, same, or worse for each intervention month Conclusion(s): GI symptoms were found to be independent of lactase treatment. In this study population with a high prevalence of lactose deficiency, IBS symptoms appeared to be independent of lactose maldigestion.	Allocation concealment: unclear Blinding: double-blinded Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	to allow adherence to frequent interviews; and 4) showed proper compliance and reliability during first (control) month. Methods to measure outcomes: Diary record of symptoms filled out daily. Symptoms included constipation, diarrhea, abdominal pain, abdominal distension, and flatulence.					
Newcomer 1983[80] RCT, crossover Sponsorship: National Dairy Council and North Carolina State University Dairy Foundation USA Duration of symptom recording: 1 week	Data source: 79 American subjects, 61 lactase sufficient subjects with IBS and 18 lactase deficient (all had histories of milk intolerance) subjects. There were also 10 healthy controls. Inclusion criteria: lactase deficiency was diagnosed by an increase in the breath hydrogen ≥0.30 ml/min above basal level after challenge of 50 g lactose in 500 ml water. IBS was diagnosed on the basis of a typical history and a minimal number of negative diagnostic studies. Methods to measure	1) Lactase deficiency subjects (n=18) Age range (18-69) Gender: not reported Race/ethnicity: not reported 2) lactase sufficient subjects with IBS (n=61) Age range (20-82) Gender: not reported Race/ethnicity: not reported 3) healthy controls (n=10) Age range (21-64) Gender: not reported Race/ethnicity: not reported	*Lactase deficient subjects* Acidophilus milk (mean 1½ glasses daily) x 1 week (either week 1 or week 4). 2 week control period between weeks of starting new treatment *Lactase sufficient subjects with IBS and controls* Acidophilus milk (3 8 oz. glasses daily) x 2 weeks (either week 3 or week 7). Three 2- week control periods (milk-drinking periods in between).	*lactase deficient subjects* Unaltered milk (mean 1½ glasses daily) x 1 week (either week 1 or week 4). *lactase sufficient subjects with IBS and controls* Unaltered milk (3 8 oz. glasses daily) x 2 weeks (either week 3 or week 7).	Cumulative symptom indices for the 18 lactase deficiency subjects Conclusion(s): There was no difference in the tolerance of the acidophilus and unaltered milks in the lactase deficient group. IBS subjects were also not helped by the ingestion of acidophilus milk.	Allocation concealment: unclear Blinding: double-blinded Intent-to-treat analyses: 100% followup Study withdrawals adequately described: no withdrawals reported

Appendix Table D8. Evidence table for blinded lactose intolerance treatment studies: Question 4 (continued)

Author, Year, Study Design, Study Sponsorship, Country, Length of Followup	Subject Selection, Data Source, Methods to Measure Outcomes, Inclusion/Exclusion Criteria	Subject Characteristics	Treatment-Active, Adherence Evaluations	Treatment-Control, Adherence Evaluations	Outcome assessment/ Results and Conclusions	Quality of the Study
	outcomes: Symptom (diarrhea, abdominal pain/cramps*, gas/flatus*, rumbling*, constipation) diary at end of each day. Diarrhea was yes/no, # stools per day. Scored as following for *: 0=no trouble; 1=slight trouble; 2=mild; 3=moderate; 4=severe. Constipation was better, same, worse.					

References for Appendix D

(Note that this set of references is different from those in the text of the report and the numbers are different.)

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