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Systematic Review

Calcium, Vitamin D, and Phosphorus Levels and Bone Health in Adults with Lactose Intolerance: A Systematic Review

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Context: *Lactose intolerance (LI) is a common condition characterized by lactase deficiency and impaired digestion of lactose. Dairy avoidance among affected individuals can reduce intakes of calcium, vitamin D, and phosphorus, with potential implications for bone health. Therefore, this review aimed to assess the effects of LI on calcium, vitamin D and phosphorus status, as well as related bone health in adults.*

Objective: *This systematic review synthesizes evidence regarding implications for bone health reported in observational studies on calcium, vitamin D, and phosphorus status in adults with LI and dairy avoidance.*

Data Sources: *PubMed, Web of Science, Scopus, and CINAHL were searched for studies from 1980 to 2024. The strategy followed the population–intervention–comparison–outcome framework and used MeSH terms with Boolean operators. Eligible designs were observational; most were cross-sectional studies and included adults (aged ≥18 years) with LI.*

Data Extraction: *Data were extracted on study characteristics, population demographics, diagnostic methods, assessment of micronutrient status, and bone outcomes. Risk of bias was assessed using the Newcastle-Ottawa Scale, adapted for cross-sectional designs.*

Data Analysis: *A narrative synthesis following the Synthesis Without Meta-analysis (SWiM) guidelines was used to compare nutritional and bone outcomes between lactose-intolerant and lactose-tolerant groups. Thirteen studies were included. Overall, study quality was mostly good or satisfactory, with few studies rated as unsatisfactory or fair. For serum calcium and phosphorus, studies generally did not demonstrate differences by LI status. Evidence on vitamin D was limited to 3 studies with heterogenous results; therefore, we cannot conclude that vitamin D status is unaffected. Conversely, LI was generally associated with significantly reduced calcium intake. Bone outcomes were inconsistent.*

Conclusions: *Given inconsistent evidence across studies, chronically low calcium intake in LI may be associated with, but not definitively causal for, adverse bone outcomes. Our findings support ensuring*

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sufficient calcium intake and highlighting the need for prospective studies.

Systematic Review Registration: PROSPERO registration No. [*CRD42024607063*].

Key words: bone health, calcium, lactose intolerance, phosphorus, vitamin D.

INTRODUCTION

Lactose intolerance (LI) is a common global health condition, characterized by the inability to digest lactose.[1] Individuals with LI present with gastrointestinal symptoms such as bloating, abdominal cramps, diarrhea, nausea, and/or vomiting after consuming lactose-containing foods.[1,2] These symptoms arise from hypolactasia, a deficiency of the β-galactosidase enzyme, which causes lactose maldigestion and results in fermentation of undigested lactose in the colon.[3] The global prevalence of LI is approximately 65%-70%[4] and varies by ethnicity and geographical, cultural, and genetic factors; for example, prevalence ranges from 2%-15% in Northern Europeans, 6%-22% in the Americas, and 95%-100% in Asia,[1] while in the Middle East, LI is common due to the low prevalence of genetic mutations that allow continued lactose production after infancy.[5] As a result, individuals with LI may reduce or avoid consumption of dairy products,[6,7] which poses a challenge to maintaining adequate dairy intake.[8]

Along with this challenge to maintaining adequate dairy intake, milk and other dairy products are a primary food source for over 6 billion people worldwide.[9] Several guidelines recommended milk and dairy intake across all ages.[10,11] Dairy products provide carbohydrates, high-quality proteins, and key minerals and vitamins, including calcium, phosphorus, and vitamin D.[11,12] These nutrients support growth and development, particularly in children.[13] Cross-sectional and cohort studies also report that milk consumption before and after puberty positively correlates with increased bone mineral density (BMD) and bone mineral content (BMC),[14] indicators of bone health, into adulthood[15,16] and old age.[17]

Inadequate calcium intake among individuals with LI has been associated with increased risks of osteoporosis and rickets, potentially impairing physical development in children and reducing bone density in adults.[6,8,18] While prior research has clarified the association between LI, reduced calcium intake, and bone health,[6,18,19] data on the effects of LI on other nutrients, such as phosphorus and vitamin D, and on broader nutritional status remain limited. Importantly, calcium and phosphorus are vital elements of bone development and their absorption is strongly influenced by vitamin D. When vitamin D is lacking, only 10%-15% of dietary calcium is absorbed; when it is sufficient, absorption rises to 30%-40%.[20] Furthermore, the compensatory mechanisms of the body that maintain serum calcium levels may be triggered by deficits in any of these elements, with potential effects on bone health and mineral balance.[20]

Individuals with LI often reduce or avoid dairy product consumption, which may lead to reduced intake of critical micronutrients such as calcium and vitamin D, thereby contributing to impaired bone health outcomes and inadequate micronutrient status.[21]

Previous studies have mostly focused on calcium intake in individuals with LI,[18] while evidence concerning vitamin D and phosphorus status remains limited and inconsistent.[21–23] Furthermore, the interactions among these micronutrients and their implications for bone health are not yet fully understood, highlighting an important knowledge gap. As a result, a comprehensive synthesis of the available evidence is required.

Evaluating these 3 micronutrients together is therefore important when assessing the effects of reduced dairy consumption in adults with LI. We focused on adults (aged ≥18 years) because lactase activity commonly declines after weaning, increasing the prevalence of LI in adulthood.[24] Given this age-related decline, adult-targeted interventions are of particular interest.[18] Children typically have higher lactase activity and distinct nutritional needs and dietary patterns.[25] Therefore, focusing on adults allows for a more consistent evaluation of bone health outcomes, as bone growth and nutritional requirements differ between children and adult populations.

The hydrogen breath test (HBT) and lactose tolerance test (LTT) are commonly used diagnostic methods for LI but have limitations, including false positives (eg, due to small intestinal bacterial overgrowth) and variability in glucose response.[26,27] Genetic testing can identify lactase persistence variants,[28] and in nutrition studies, objective methods are preferred because self-reported LI may introduce misclassification and influence dietary and micronutrient assessments.[27]

Therefore, this review focuses on participants with a confirmed clinical diagnosis of LI. The findings aim to inform clinical practice and dietary recommendations for adults with LI.

This review offers several contributions that to our knowledge have not been reported in previous publications, such as updates of the database through 2024,

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which includes studies using objective diagnostic criteria for LI, and incorporation of phosphorus-related findings. Together, these features enhance the value, rigor, and relevance of the current review.

This systematic review evaluated current evidence on calcium, vitamin D, and phosphorus status and their association with bone health outcomes in adults with LI.

The research question addressed was: What is the association between calcium, vitamin D, and phosphorus status and bone health outcomes in adults with LI?

METHODS

Search Strategy and Data Sources

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42024607063) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[29] The research question and search strategy were developed using the population, intervention, comparison, and outcome (PICO) framework to define key concepts, as shown in Table 1. Medical Subject Headings (MeSH) terms were used to identify core keywords, and Boolean operators ("AND" and "OR") structured the search logic.

An initial pilot search in PubMed evaluated the relevance of preliminary search terms, including "lactose intolerance," "milk intolerance," "lactase deficiency," and "nutritional status." Results informed refinement of search terms and the inclusion of additional synonyms. Filters for study design (eg, randomized controlled trials, observational studies) and publication year were applied to improve precision and recall. The final search strategy was then applied to multiple databases, including Web of Science, Scopus, and CINAHL (via EBSCO), to ensure comprehensive coverage (Table 2).

Rayyan software, a free web-based tool for screening systematic reviews developed by the Qatar Computing Research Institute, part of the Qatar Foundation for Education, Science, and Community Development, was used to manage references and streamline screening, enabling efficient identification and organization of eligible studies. Studies published during 1980 through 2024 were included. Supplementary material 1 contains full search strategies for each database.

Eligibility Criteria

Eligibility was determined using the PICOS framework. Studies were included if they were observational in design (cross-sectional, cohort, or case-control), included adults (aged ≥18 years) with a clinically confirmed diagnosis of LI, compared individuals with and those without

Table 1. PICOS Criteria Used to Define the Review Question[a]

Element	Description
Intervention/Exposure (I)	Adults with a clinically confirmed diagnosis of lactose intolerance
Comparison (C)	Adults without lactose intolerance
Outcomes (O)	primary outcomes—micronutrient level (calcium, vitamin D, and phosphorus), assessed via dietary intake and/or biochemical markers secondary outcomes—bone health indicators, including BMD, BMC, fracture incidence, osteoporosis, and bone turnover biomarkers
Study design (S)	Observational studies (cross-sectional, cohort, or case-control)

Abbreviations: BMC, bone mineral concentration; BMD, bone mineral density.
[a]This table presents the participant characteristics, intervention definitions, comparators, outcomes, and research design used to determine the eligibility criteria.

Table 2. Main Keywords Applied Across Databases[a]

"Lactose intolerance" or "dairy intolerance" or "milk intolerance" or "milk sugar intolerance" or "dairy product intolerance" or "lactase non-persistence" or "lactose malabsorption" or "lactase deficiency" or "alactasia" or "hypolactasia"
AND
"Nutritional status" or "nutrition status" or "food intake" or "dietary intake" or "nutrient intake" or "nutritional intake" or "feed intake" or "micronutrient intake" or "micronutrient intakes" or "macronutrient intake" or "ingestion" or "malnourishment" or "undernutrition" or "nutritional deficiency" or "hypernutrition" or "overnutrition" or "vitamin D" or "25-hydroxyvitamin D" or "vitamin D intake" or "vitamin D consumption" or "dietary vitamin D" or "calcium" or "calcium intake" or "calcium consumption" or "dietary calcium" or "phosphorus" or "phosphorus intake" or "phosphorus consumption" or "dietary phosphorus"
AND
"Bone mineral density" or "bone mineral content" or "bone fracture" or "broken bones" or "osteoporosis"

[a]This table presents the main key words searched across all included databases.

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LI, and reported the following outcomes: primary outcomes, including micronutrient levels (calcium, vitamin D, and phosphorus), assessed via dietary intake and/or biochemical markers; and secondary outcomes, including bone health indicators such as BMD, BMC, fracture incidence, osteoporosis, and bone turnover biomarkers, which may be impacted by dairy avoidance; and had no language restrictions (translations performed with Google Translate when necessary). Studies were excluded if they could not be accessed in full because they were not open-access publications; were nonresearch publications (eg, opinion pieces, editorials, conference abstracts, book chapters); or included individuals (aged <18 years), or relied on self-reported LI without physiological confirmation. Three reviewers collaboratively screened titles, abstracts, and full texts; inclusion/exclusion decisions were resolved by consensus.

Study Selection and Data Extraction

The first author (A.M.) applied the selection criteria to identify relevant studies on LI and nutritional status. Titles and abstracts were screened in Rayyan using predefined inclusion and exclusion criteria. Publications were selected for full-text review if deemed relevant, potentially relevant, or if eligibility was uncertain. Disagreements regarding eligibility of an article were discussed and resolved by consensus. T.A., V.R., and A.M. conducted the full-text evaluation to confirm eligibility.

Data were extracted by A.M. and T.A., and V.R. cross-checked for accuracy and consistency. Data extraction was completed using a detailed, predefined data extraction form capturing the following information: Study characteristics (author name, year of publication, study location, and study design); sample characteristics (sample size, age range, sex, and diagnostic criteria for LI); methodology (diagnostic methods for LI and approaches to assessing micronutrient status and bone health); outcomes (micronutrient status—calcium, vitamin D, and phosphorus; and bone health measures—BMD, BMC, fractures, osteoporosis, and bone turnover biomarkers); and results (findings for these outcomes in individuals with LI, including comparisons with controls). This structured approach ensured consistent eligibility application and reliable data extraction for each included study.

Risk of Bias Assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS), designed to evaluate the quality of nonrandomized observational research.[30,31] The NOS was chosen because it provides a structured appraisal of observational studies; alternatives such as AMSTAR-2 were less applicable to individual studies. The NOS evaluates quality across 3 domains—selection, comparability, and outcome (for cohort studies) or exposure (for case-control studies). Studies were rated as good, fair, or poor based on the distribution of stars across these domains. For cross-sectional studies, the scale was adapted to reflect key methodological features of that design. Scores were assigned according to established thresholds (Very good, 9-10; Good, 7-8; Satisfactory, 5-6; Unsatisfactory, 0-4). One reviewer performed the initial quality assessments, which were then discussed and confirmed with the other 2 team members to reach consensus. Additionally, because most included studies were cross-sectional in design, the NOS was preferred over GRADE because it validated for assessing the quality of observational studies, at individual study level.[32]

RESULTS

Search Results

Narrative Synthesis. Due to methodological and statistical heterogeneity, differences in diagnostic standards, measurement units, reporting formats, and variability in study results, a meta-analysis was not feasible. These discrepancies prevented calculation of equivalent effect sizes for pooled synthesis. Instead, a narrative synthesis was conducted following the Synthesis Without Meta-analysis guidelines.[33] The synthesis summarized key study descriptors (year, country, sample characteristics, and diagnostic methods) and findings on nutrient intake/status and bone health in lactose-intolerant vs lactose-tolerant groups.

A comprehensive search initially identified 496 records (Figure 1). After removing duplicates, 202 records remained for title and abstract screening. Following detailed evaluation, 196 were excluded for the following reasons: genetic focus ($n = 12$), irrelevant study design ($n = 101$), irrelevant outcomes ($n = 23$), non-target populations ($n = 22$), or publication before 1980 ($n = 4$).

Subsequently, 40 articles were selected for full-text review. Of these, 27 were excluded due to irrelevant outcomes ($n = 19$), reliance on self-reported diagnosis ($n = 7$), or non-English language (no access to the full text) ($n = 1$) (see Supplementary Material 2).

Ultimately, 13 studies met the eligibility criteria and were included in the final systematic review.[8,34–44] A manual search of reference lists did not yield additional studies. Figure 1 presents the PRISMA flow chart of study selection and inclusion.

Characteristics of the Reviewed Studies. The 13 included studies varied in design, population characteristics,

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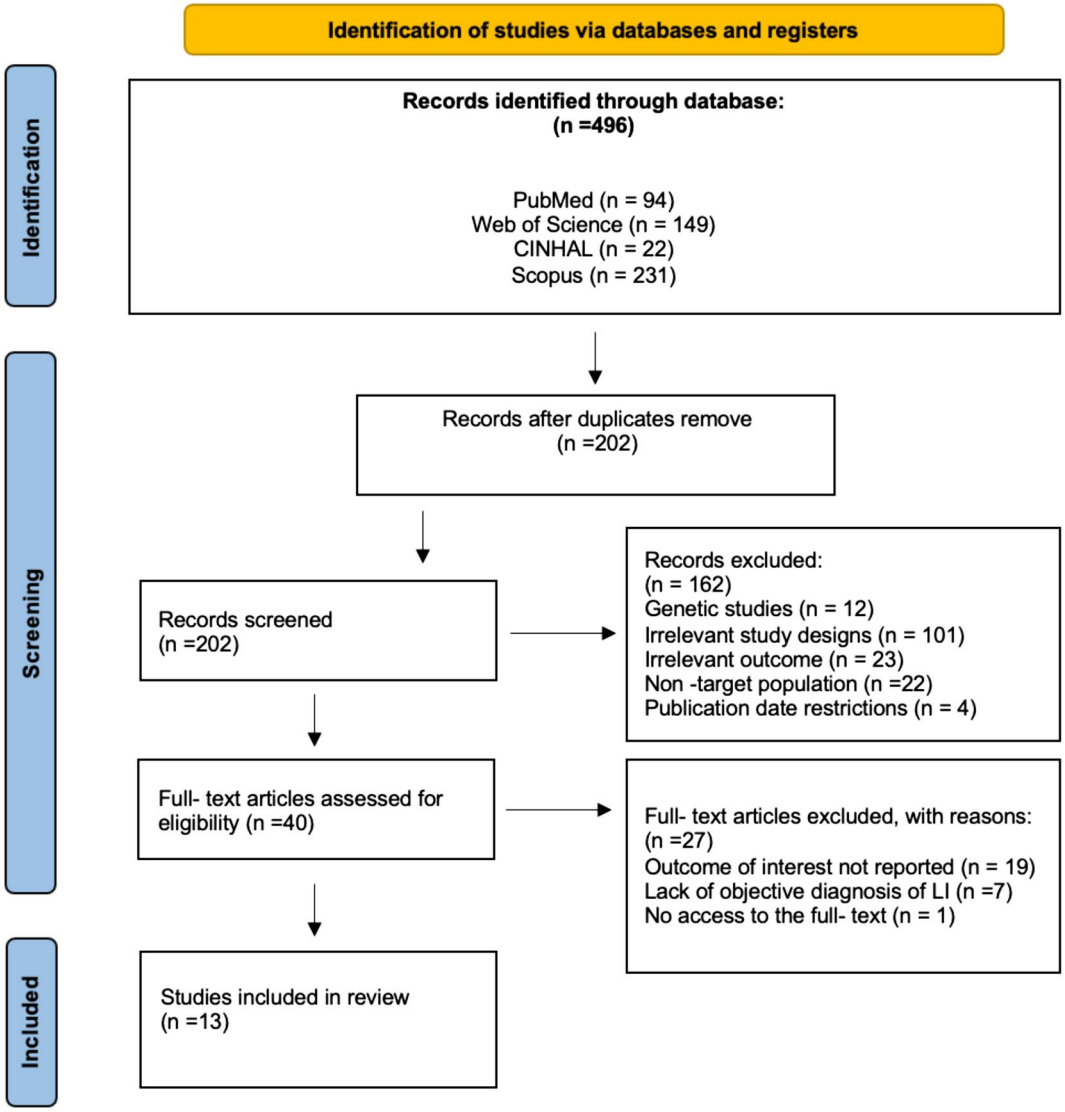

Figure 1. PRISMA Flow Diagram. This figure represents the number of records detected, screened, excluded, and included in the final review

settings, diagnostic approaches to LI, and reported outcomes on nutrient intake and bioavailability (Table 3).

Geographically, 3 studies were conducted in Italy,[42–44] 3 in Austria,[38,40,41] 2 in Malaysia,[8,39] and 1 each in Australia,[37] the United States,[36] Israel,[35] Brazil,[45] and India.[34] Twelve studies were cross-sectional, and 2 were case-control studies.[38,41] No cohort studies met the inclusion criteria.

The total sample size across studies was 1547, with individual samples ranging from 23 to 342 participants; mean ages spanned 22.5[8] to 70.3 years.[36] All studies included female participants; 7 focused exclusively on women, particularly postmenopausal women,[34,36,37,41,43–45] whereas the remaining 6 studies included both sexes. Some studies reported ethnicity, such as White Caucasians[34,36,37,43,44] and Asian groups (Malays, Indians, and Chinese[8,39]) (Table 3).

Validated diagnostic methods for LI were employed. The LTT was the sole method in 2 studies,[36,45] whereas the HBT was the sole method in 6 studies.[8,34,35,40,43,44] Five studies used a combination of LTT and HBT with symptom assessment to increase diagnostic accuracy.[37–39,41,42]

Micronutrient status was assessed using diverse methods. Six studies reported serum markers (calcium, phosphorus, and vitamin D).[35–38,40,42] However, only 3 provided vitamin D outcomes suitable for between-group comparison, and their findings were heterogeneous; accordingly, conclusions about vitamin D status in LI remain uncertain.[35,37,42] Calcium intake was evaluated using food records or diaries and dietary questionnaires on milk, dairy, and overall dietary patterns.[42,43,45] Two studies used a validated food frequency questionnaire (FFQ) to estimate intake of calcium-rich foods.[8,35]

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Table 3. Characteristics of Included Studies, Arranged Chronologically by Year of Publication[a]

Author(s)/ Year	Setting	Study design	Aim of study	Sample characteristics						LI diagnostic method	Measured outcomes	Methods used
				Sample size	Case	Control	Age, y (mean ± SD)	Gender	Ethnicity			
Finkenstedt et al. (1986)[41]	Austria	Case-control study	Evaluated the prevalence of dairy calcium consumption and LM in women with osteoporosis compared to age-matched controls.	$n = 66$	Osteoporotic women	Controls	cases: 54 y[31–65] (SD:NR) Controls: 56 y[33–67] (SD:NR)	F	NR	LM:LTT LI: Assessed through a questionnaire on the history of milk intolerance	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (osteoporosis)	• Dietary questionnaire • X-ray, trabecular index (< 54), spontaneous
Horowitz et al. (1987)[37]	Australia	Cross-sectional comparative observational study	Assess the prevalence of lactase deficiency, examine calcium and lactose malabsorption, and compare bone mineral density in postmenopausal osteoporotic females.	$n = 46$ (postmenopausal with osteoporosis)	Lactose malabsorbers	Normal absorbers	cases: 65 ± 1 y Controls: 66 ± 2 y	F	White (Northern/ Western European)	LM: HBT LI: Assessed based on participant-reported symptoms	• Micronutrient level: (vitamin D) • Dietary assessment (calcium intake) • Bone health (urinary hydroxyproline-to-creatinine ratio, BMD)	• Competitive protein-binding test • Dietary questionnaire • Bergman and Loxley's method, photon absorptiometry, GE8000 scanner
Vigorita et al. (1987)[36]	United States	A comparative cross-sectional observational study with histomorphometric analysis	Investigating lactose tolerance and analysing bone biopsies histomorphometrically in postmenopausal women with osteoporotic spinal compression fractures.	$n = 23$ (postmenopausal with spinal osteoporosis)	Lactase deficient	Normal	cases: 70.3 (SD: NR) control: 66.3 (SD: NR)	F	Northern and eastern European origins	LTT	• Micronutrient level: (vitamin D, calcium, phosphorus) • Dietary assessment (calcium intake) • Bone health (osteoclast count, alkaline phosphatase)	• Laboratory tests • Dietary history questionnaire • Histomorphometry of bone biopsies
Callegari et al. (1990)[43]	Italy	Cross-sectional study	Examine the relationship between bone mineral content in postmenopausal women and lactose malabsorption, milk consumption, and calcium intake.	$n = 155$ (postmenopausal)	Lactose malabsorbers	Absorbers	52.5 y (SD: NR; range 35-72 y)	F	Caucasian	HBT	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (BMC)	---- • 2-day dietary record • Bone mineral analyser with photon absorptiometry

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Table 3. Continued

Author(s)/ Year	Setting	Study design	Aim of study	Sample characteristics						LI diagnostic method	Measured outcomes	Methods used
				Sample size	Case	Control	Age, y (mean ± SD)	Gender	Ethnicity			
Pietschmann et al. (1991)[38]	Austria	Case-control study	Evaluate the serum levels of osteocalcin in individuals with dietary-treated lactase insufficiency in comparison to controls to evaluate bone turnover when calcium intake is low.	$n = 30$	Lactase- deficient patients	Controls	46 ± 5 y	M/F 4/6	NR	HBT and LTT	• Micronutrient level: (calcium, phosphorus) • Dietary assessment (calcium intake) • Bone health (serum osteocalcin, alkaline phosphatase)	• Routine blood chemistry • 3-day dietary record • Radioimmunoassay for serum osteocalcin and routine blood chemistry for alkaline phosphatase
Slemenda et al. (1991)[34]	India	Case-control study	Examine the possible contribution of lactase deficiency to the development of low bone mass in adult female twins.	$n = 342$	Lactase deficient	Lactase persistent	44.1 ± 12 y (NR for groups)	F	White population	HBT	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (BMD)	------ • NR • SPA, DPA
Corazza et al. (1995)[44]	Italy	Cross-sectional study	Investigate a population with a higher rate of LM and use a physiological lactose dose in order to give more information about the function of LM in postmenopausal osteoporosis.	$n = 58$ (Italian postmenopausal women)	Malabsorbers with symptoms of intolerance	Lactose absorbers	57 ± 7 y	F	Italian	HBT	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (BMD)	------ • Dietary diary • DPA
Di Stefano et al. (2002)[42]	Italy	Cross-sectional study	Assess if LI prevents young individuals from reaching a sufficient peak bone mass.	$n = 103$	Intolerant	Absorbers	Cases: 27 ± 2 y Controls: 28 ± 3 y	M/F 44/59	NR	HBT and participant-reported symptoms	• Micronutrient level: calcium and vitamin D • Dietary assessment (calcium intake) • Bone health (turnover, BMD, BMC)	• Serum analysis • Dietary diary for 3 days • Blood analysis, DEXA
Kudlacek et al. (2002)[40]	Austria	Cross-sectional study	Evaluate if there are any variations in the clinical behaviour, fracture risk, and BMD among individuals with LI.	$n = 218$	LI	Controls	Cases (2 LI subgroups): 57.1 ± 12.2 / 58.2 ± 12.7 y Controls: 58.6 ± 10.5 y	M/F 43/175	NR	HBT	• Micronutrient level: (calcium) • Dietary assessment (calcium intake) • Bone health (BMD, fracture incidence and mineral biomarkers such as alkaline phosphatase)	• Routine blood chemistry tests • Questionnaire • SPA, qCT, DEXA, and routine blood chemistry tests

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Table 3. Continued

Author(s)/ Year	Setting	Study design	Aim of study	Sample characteristics						LI diagnostic method	Measured outcomes	Methods used
				Sample size	Case	Control	Age, y (mean ± SD)	Gender	Ethnicity			
Segal et al. (2003)[35]	Israel	Cross-sectional study	Assess how LI affects quantitative bone parameters in the appendicular and axial skeletal sites. Also, evaluate how quantitative bone parameters in LI patients are affected by calcium intake from dairy and non-dairy food sources, calcium-regulating hormones, and bone turnover.	$n = 66$ (patients with LI)	Men vs premenopausal women vs postmenopausal women	None	NR ± NR (age range 20-78 y)	M/F 17/49	NR	HBT	• Micronutrient level: (vitamin D) • Dietary assessment (calcium intake) • Bone health (BMD)	• Blood analysis • Semi-quantitative FFQ • DEXA, QUS
Salomão et al. (2012)[45]	Brazil	Cross-sectional study	Assess the differences in calcium consumption and BMD between women with LI and controls.	$n = 60$	LI	Non-LI	(SD: NR; range 20-40 y)	F	NR	LLT	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (BMD)	------ • 3 24-hour dietary recalls • DEXA
Yahya et al. (2016)[39]	Malaysia	Cross-sectional study	Examine the prevalence of LI and its relationship to bone mineral density among university students in Malaysia.	$n = 100$ (students)	LI	Non-LI	23.9 ± 4.7 y	M/F 50/50	Malay	HBT and LTT	Bone health (BMD)	• QUS
Yahya et al. (2021)[8]	Malaysia	Cross-sectional study	Evaluate the prevalence of LI, calcium intake, and physical activity levels, as well as investigate the relationship between these factors and the bone health condition of young people	$n = 300$ (students)	Lactose intolerant	Lactose tolerant	22.5 ± 3.2 y	M/F 150/150	Chinese, Indian, and Malay	HBT	• Micronutrient level: none • Dietary assessment (calcium intake) • Bone health (BMD)	-------- • Semi-quantitative FFQ • QUS

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; DEXA, Dual-energy X-ray absorptiometry; DPA, Dual photon absorptiometry; F, Female; FFQ, Food Frequency Questionnaire; HBT, Hydrogen breath test; LI, Lactose intolerance; LM, Lactose malabsorption; LTT, Lactose tolerance test; M, Male; NR, Not reported; qCT, Quantitative computed tomography; QUS, Quantitative ultrasound; SPA, Single-photon absorptiometry.

[a]This table provides an overview of the key characteristics of the included studies, including author[s] name, year of publication, study location, and study design; sample characteristics; methods used for diagnosing LI; and measured outcomes.

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Bone Health Assessment Methods

The studies used a range of imaging modalities and analytical techniques to evaluate bone health. Two studies employed quantitative ultrasound at peripheral sites to assess bone properties and infer bone quality.[8,39] One study used histomorphometric analysis of bone biopsies to examine bone remodeling and microarchitecture.[36] Another study used dual-photon absorptiometry to quantify BMD.[44] A bone mineral analyzer employing photon absorptiometry was used in 1 study.[43]

Seven studies combined multiple bone measurement methods to provide a comprehensive assessment of bone health.[34,35,37,38,40–42] These included single-photon absorptiometry, quantitative computed tomography, dual-energy X-ray absorptiometry, and radiographic evaluation for detailed assessment of BMD and structural integrity. Additional techniques comprised dual-photon absorptiometry, quantitative ultrasound, trabecular index calculations with X-ray imaging to identify spontaneous fractures, the Bergman and Loxley method, and the GE8000 scanner. Complementary biochemical analyses of bone turnover markers (eg, alkaline phosphatase and osteocalcin) were also reported.

Effect of Lactose Intolerance on Serum Calcium, Vitamin D and Phosphorus Levels

Serum Calcium Level. Four studies assessed serum calcium levels in individuals with LI compared with controls.[36,38,40,42] None reported significant differences between-group differences. Mean calcium values across all studies were within the adult reference range (8.6-10.2 mg/dL).[46] (Table 4).

Serum Phosphorus Level. Two studies evaluated serum phosphorus levels.[36,38] Pietschmann et al.[38] compared individuals with LI and controls, whereas Vigorita et al.[36] compared postmenopausal women with LI and osteoporosis with healthy controls. Neither study found significant differences. Mean phosphorus values were within the adult reference range (2.5-4.5 mg/dL)[47] indicating no evidence of deficiency (Table 4).

Serum Vitamin D Level. Only 3 studies reported vitamin D outcomes, with inconsistent findings (Table 5).[35,37,42] Di Stefano et al.[42] reported higher mean serum vitamin D concentrations in individuals with LI than in controls, whereas Segal et al.[35] (no control group) found that 22% of participants with LI had low vitamin D (5% deficient; 17% insufficient). Horowitz et al.[37] reported no significant difference between postmenopausal women with LI and osteoporosis and controls. None of these studies reported *P*-values for vitamin D comparisons.

Dietary Calcium Intake in Adults with Lactose Intolerance

Most included studies assessed dietary calcium intake.[8,34–38,40–45] Eight studies demonstrated significantly lower calcium intake among individuals with LI than controls.[36–38,40–42,44,45]

Corazza et al.[44] reported that participants with lactose malabsorption and symptoms consumed less calcium from milk and dairy (378 ± 220 mg/d) than those without (511 ± 313 mg/d; $P < .005$). Notably, both groups were below the IOM/NAM (2011) Dietary Reference Intake recommendations. (1000 mg/d for adults; 1200 mg/d for those aged >70 years).[48] Similar trends were noted elsewhere (Table 6).[36–38,40–42]

Two studies[35,43] found lower intake in the LI group but without statistical significance, and Callegari et al.[43] did not report exact intake values for postmenopausal women with LI.

Conversely, Slemenda et al.[34] and Yahya et al.[8] reported no significant between-group differences ($P = .19$ and $P = .937$, respectively).[8,34]

Effect of Lactose Intolerance on Bone Health

Bone Marrow Density. Five studies, using different assessment methods and anatomical sites, found no significant differences in BMD between lactose-intolerant and control groups.[8,34,37,39,40]

Horowitz et al.[37] compared postmenopausal women with osteoporosis and healthy controls and observed similar vertebral mineral density (65 ± 8 vs 67 ± 7 mg/mL) and forearm mineral density (286 ± 15 vs 303 ± 17 mg/mL). Slemenda et al.[34] likewise reported no significant differences between cases and controls in BMD at the spine ($P = .45$) and the femoral neck ($P = .19$). These findings are consistent with those of 3 other studies.[8,39,40] Yahya et al.[39] and Kudlacek et al.[40] reported BMD using T-scores, and Yahya et al.[8] additionally, incorporated broadband ultrasound attenuation measurements (Table 7).

In contrast, 4 studies[35,42,44,45] reported significantly lower BMD among individuals with LI at various skeletal sites. Salomão et al.[45] found that BMD at the femoral neck and total femur was significantly lower in the LI group than in the controls ($P < .05$), whereas whole-body BMD showed no significant difference. Corazza et al.[44] reported significantly lower *z* scores in postmenopausal women with LI ($P < .05$). Similarly, Di Stefano et al.[42] observed significantly lower T- and *z* scores at both the femoral neck and lumbar spine in participants with LI compared with controls ($P < .01$). Similar trends were noted elsewhere (Table 6).[35,42]

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Table 4. Serum Calcium and Phosphorus Level of Adults

Study	Nutrient assessed	Levels		*P* value
		Lactose-intolerant group	Control group	
Vigorita et al. (1987)[36¡]	Calcium (mg/dL)	8.9-10.1	8.2-10.1	NS
	Phosphorus (mg/dL)	2.7-4.7	3.1-3.9	NS
Pietschmann et al. (1991)[38]	Calcium (mmol/L)	2.4 ± 0.04	2.4 ± 0.03	NS
	Phosphorus (mmol/L)	1.2 ± 0.1	1.1 ± 0.05	NS
Di Stefano et al. (2002)[42]	Calcium (mmol/L)	2.31 ± 0.15	2.39 ± 0.15	NS
Kudlacek et al. (2002)[40]	Calcium (mmol/L)	2.3 ± 0.23 (mild LI), 2.3 ± 0.21 (severe LI)	2.36 ± 0.1	NS

Abbreviations: LI, lactose intolerance; NS, no significant difference (p, not reported by the original study); ¡, Postmenopausal women with osteoporosis.
[a]This table illustrates the findings on serum calcium and phosphorus levels of adults across the included studies.

Table 5. Serum Vitamin D Levels of Adults[a]

Study	Vitamin D levels		*P* value
	Cases	Controls	
Horowitz et al. (1987)[37¡]	72 ± 8 nmol/L	59 ± 7 nmol/L	NS
Di Stefano et al. (2002)[42]	35 ± 9 ng/mL	29 ± 9 ng/mL	NS (within sufficient range 30-100 ng/mL)[68]
Segal et al. (2003)[35]	5% were classified as deficient and 17% as insufficient.	---	NR

Abbreviations: NR, not reported; NS, no significant difference (p: not reported by the original study); ¡, postmenopausal women with osteoporosis.
[a]This table illustrates the findings on serum vitamin D levels of adults across the included studies.

Table 6. Dietary Calcium Intake of Adults[a]

Study	Calcium intake (mg/d)		*P* value
	Cases	Controls	
Finkenstedt et al. (1986)[41#]	125 ± 20 (from milk)	252 ± 43 (from milk)	$P < .05$
Horowitz et al. (1987)[37¡]	1.6 ± 0.2 L/week (milk intake)	3.2 ± 0.7 L/week	$P < .025$
Vigorita et al. (1987)[36¡]	420 ± 218	653 ± 348	$P < .05$
Callegari et al. (1990)[43*]	Lower calcium intake (exact values not provided)	NR	NS
Pietschmann et al. (1991)[38]	90 ± 30	NR	Significant (exact p-value not provided)
Slemenda et al. (1991)[34]	604 ± 341	677 ± 377	$P = .19$
Corazza et al., (1995)[44*]	378 ± 220	511 ± 313	$P < .005$
Di Stefano et al. (2002)[42]	685 ± 88	902 ± 88	$P < .001$
Kudlacek et al. (2002)[40]	188 (mild LI), 167 (severe LI)	212	$P < .05$
Salomão et al. (2012)[45]	250.5 ± 111.7	659.7 ± 316.1	$P < .05$
Segal et al. (2003)[35]	692 ± 162	NR	---
Yahya et al. (2021)[8]	546.41 ± 389.64	558.23 ± 387.43	$P = .937$

Abbreviations: LI, lactose intolerance; NS, no significant difference (p, not reported by the original study); NR, not reported; #, individuals with osteoporosis; *, postmenopausal women; ¡, postmenopausal women with osteoporosis.
[a]This table illustrates the findings on calcium intake of adults across the included studies.

Bone Mineral Content. Three studies investigated BMC.[40,42,43] Callegari et al.[43] reported significantly lower BMC at the mid-diaphysis of the radius in postmenopausal women with LI vs controls ($P < .03$). Di Stefano et al.[42] observed reduced BMC in individuals with LI compared with those without, and the differences were statistically significant across all measured sites ($P < .01$; Table 8). However, Kudlacek et al.[40] found no significant differences

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Table 7. Bone Mineral Density of Adults[a]

Study	BMD measurement	BMD		*P* value
		Case	Control	
Horowitz et al. (1987)[37¡]	Vertebral BMD (mg/mL)	65 ± 8	67 ± 7	NS
	Forearm BMD (mg/mL)	286 ± 15	303 ± 17	
Slemenda et al. (1991)[34]	Spine BMD (g/cm^2)	1.129 ± 0.185	1.148 ± 0.154	$P = .45$
	Femoral neck BMD (g/cm^2)	0.844 ± 0.120	0.872 ± 0.140	$P = .19$
Corazza et al. (1995)[44]*	BMD (*z* scores)	−1.5 ± 0.7	−0.9 ± 0.8	$P < .05$
Di Stefano et al. (2002)[42]	BMD T-score (lumbar spine)	−0.80 ± 0.7	−0.12 ± 0.6	$P < .01$
	BMD T-score (femoral neck)	−0.75 ± 0.7	−0.05 ± 0.6	
	BMD *z* score (lumbar spine)	−0.78 ± 0.7	0.10 ± 0.6	
	BMD *z* score (femoral neck)	0.70 ± 0.7	0.06 ± 0.6	
Kudlacek et al. (2002)[40]	BMD (mg/cc)	Mild LI: 109.8 ± 35 Severe LI: 107.7 ± 36	111.2 ± 31.2	NS
Segal et al. (2003)[35]	BMD z score (lumbar spine)	Postmenopausal women: −0.87 ± 0.22 Men: −1.32 ± 0.65	NR	$P = .004$ $P = .015$
		Premenopausal women: 0.59 ± 0.81		NS
Salomão et al. (2012)[45]	BMD (femoral neck)	0.77 ± 0.12	0.86 ± 0.13	$P < .05$
	BMD (Total Femur)	1.06 ± 0.12	1.14 ± 0.14	
	BMD (Whole Body)	1.08 ± 0.09	1.14 ± 0.15	NS
Yahya et al. (2016)[39]	BMD (T-scores)	1.16 ± 1.42	0.52 ± 1.11	$P = .264$
Yahya et al. (2021)[8]	BUA (dB/MHz)	96.59 ± 16.74	98.89 ± 16.95	$P = .245$
	BMD (T-score)	0.61 ± 1.35	0.79 ± 1.36	$P = .249$

Abbreviations: BMD, bone mineral density; BUA, broadband ultrasound attenuation; dB, decibel; LI, lactose intolerance; MHz, megahertz; NS, no significant difference (p, not reported by the original study); NR, not reported; *, Postmenopausal women; ¡, Postmenopausal women with osteoporosis.
[a]This table illustrates the findings on bone mineral density of adults across the included studies.

Table 8. Bone Mineral Content of Adults[a]

Study	BMC Measurement	Bone mineral content		*P* value
		Case	Control	
Callegari et al. (1990)[43]*	MP density (mg/cm^2)	641.1 ± 80.00	675.7 ± 58.3	$P < .03$
Di Stefano et al. (2002)[42]	Lumbar spine	36.1 ± 4.9	39.9 ± 4.3	$P < .01$
	Femoral neck	5.2 ± 0.9	6.9 ± 1.0	
Kudlacek et al. (2002)[40]	Radial BMC (arbitrary units)	Mild LI: 33 ± 8 Severe LI: 33.7 ± 11.3	35 ± 9	*NS*

Abbreviations: BMC, bone mineral content; LI, lactose intolerance; MP, Middle point; NS, no significant difference (p, not reported by the original study); *, Postmenopausal women.
[a]This table illustrates the findings on bone mineral content of adults across the included studies.

between groups (33 ± 8 and 33.7 ± 11.3 U in mild and severe LI, respectively, vs 35 ± 9 U in controls).

Incidence of Fractures. Only 1 study directly reported fracture incidence.[40] Individuals with severe LI had a significantly higher fracture rate (0.58 ± 1.07) than controls (0.28 ± 0.63; $P < .05$), whereas those with mild LI had a lower rate (0.11 ± 0.4). Given the limited evidence, further research is needed to evaluate fracture risk in this population.

Osteoporosis. Two studies[42,44] suggested an increased risk of osteoporosis in individuals with LI based on lower BMD and related indices; however, neither study directly measured osteoporosis incidence, relying instead on surrogate markers (BMD and bone turnover indicators).

Bone Turnover Biomarkers. *Histological biomarkers.* Vigorita et al.[36] reported significantly elevated osteoid volume and osteoid seam width in individuals with LI, indicating increased bone formation or a remodeling imbalance.

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Tetracycline labeling, a marker of bone mineralization activity, was significantly higher in participants with LI (40.0 ± 13.3%) than in controls (10.8 ± 8.3%; $P < .0005$). However, osteoclast density (osteoclasts/mm) did not differ significantly between groups, suggesting bone resorption was not a major contributor.[36]

Biochemical biomarkers (serum/metabolism). No significant differences in serum alkaline phosphatase were observed between the LI and control groups.[36,38,40] However, Pietschmann et al.[38] reported significantly higher serum osteocalcin in individuals with LI than in controls ($P < .03$), suggesting increased bone turnover.

Urinary biomarkers. Di Stefano et al.[42] found significantly elevated levels of carboxy-terminal telopeptide of type I collagen in individuals with LI compared to those in controls ($P < .05$), whereas Horowitz et al.[37] reported no significant differences in the hydroxyproline/creatinine ratio between groups (Table 9).

Subgroup Patterns Across Studies

Several subgroup differences were found among the included studies. Most included studies had disproportionately more women than men, which may have introduced sex-related bias and restricted generalizability. However, regarding sex differences, some populations showed sex-based disparities in absolute BMD; for instance, Yahya et al.[39] reported that men had significantly higher T-scores despite similar LI prevalence. This biological variability is irrelevant to LI and does not explain disparities across LI studies. In contrast, studies found no difference in bone findings between the sexes.[35,40,42] Additionally, studies with younger participants often found no correlation between LI and bone outcomes,[39] whereas older or postmenopausal participants were more frequently found to have lower bone outcomes.[35,44] Nevertheless, 1 study in postmenopausal women reported no significant difference in BMD between LI participants and age-matched healthy participants.[37] Furthermore, regarding the geographic and ethnic settings, the 2 Malaysian studies yielded different results, perhaps due to differences in sample composition (1 Malay-only vs 1 mixed-ethnicity sample).[8,39] Last, bone assessment tools such as DEXA-based studies reported inconsistent results,[35,40,42] whereas QUS-based studies consistently reported no association.[8,39]

Study Quality Assessment Using the Newcastle-Ottawa Scale. Study quality varied across the included publications (Tables 10 and 11). Five studies were rated as "good" due to robust methodology, clear inclusion/exclusion criteria, effective confounder control, and valid outcome assessments.[34,36,40,42,43]

Five studies were rated as "satisfactory," with acceptable methodological quality but some limitations in comparability or risk of selection bias.[8,39,44,45]

One study was rated "unsatisfactory" due to significant methodological concerns,[37] and others were rated as "fair" due to moderate risk of bias or insufficient control of confounding.[38,41]

DISCUSSION

Key Findings

In this systematic review, we assessed the effects of LI on calcium intake; serum levels of vitamin D, calcium, and phosphorus and the bioavailability of these essential nutrients; and related bone health outcomes in adults. The included studies primarily focused on calcium intake and levels of vitamin D, calcium, and phosphorus, with limited direct evaluation of bone health markers. Most included studies were observational in design, which may have limited causal inference and affected the strength of the evidence. The evidence suggests that while serum

Table 9. Bone Turnover Biomarkers of Adults[a]

Study	Biomarker	Bone turnover biomarkers		*P* value
		Cases	Controls	
Vigorita et al. (1987)[36¡]	Osteoclast density (osteoclasts/mm)	4.2 ± 4.8	5.6 ± 5.3	NS
	Osteoid volume (%)	2.0 ± 1.3	0.9 ± 0.6	$P < .005$
	Osteoid seam width (microns)	11.7 ± 6.7	6.8 ± 3.6	$P < .0125$
	Tetracycline labeling (%)	40.0 ± 13.3	10.80 ± 8.30	$P < .0005$
	Alkaline phosphatase (IU/L)	40 to 165	33 to 106	NS
Horowitz et al. (1987)[37¡]	Urinary hydroxyproline/creatinine ratio	0.022 ± 0.001	0.023 ± 0.002	NS
	Osteocalcin (ng/mL)	8.3 ± 0.8	6.3 ± 0.4	$P < .03$
Pietschmann et al. (1991)[38]	Alkaline phosphatase (U/L)	103 ± 9	103 ± 8	NS
Di Stefano et al. (2002)[42]	ICTP (μg/L)	3.8 ± 0.9	2.3 ± 0.3	$P < .05$
Kudlacek et al. (2002)[40]	Alkaline phosphatase (U/L)	Mild LI: 111.7 ± 75 Severe LI: 103.7 ± 29	105.6 ± 35	NS

Abbreviations: ICTP, Carboxy-terminal telopeptide of type I collagen; LI, lactose intolerance; NS, no significant difference (p, not reported by the original study); ¡, Postmenopausal women and osteoporosis.
[a]This table illustrates the findings on bone turnover biomarkers of adults across the included studies.

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Table 10. Study Quality Assessment Using the Newcastle–Ottawa Scale for Cross-Sectional Studies[a]

Study	Selection				Comparability	Outcome		Quali- ty Score	Level of evidence[b]
	Representativeness of the cases	Sample size	Non-response rate	Ascertainment of the screening/ surveillance tool		Assessment of the outcome	Statistical test		
Vigorita et al. (1987)[36]	1	1	0	2	0	2	1	7	Good
Horowitz et al. (1987)[37]	0	0	0	2	0	2	0	4	Unsatisfactory
Callegari et al. (1990)[43]	1	1	0	2	0	2	1	7	Good
Corazza et al. (1995)[44]	1	0	0	2	0	2	1	6	Satisfactory
Di Stefano et al. (2002)[42]	1	0	0	2	1	2	1	7	Good
Kudlacek et al. (2002)[40]	1	0	0	2	1	2	1	7	Good
Segal et al. (2003)[35]	1	0	0	2	1	0	1	5	Satisfactory
Salomão et al. (2012)[45]	0	0	0	2	0	2	1	5	Satisfactory
Yahya et al. (2016)[39]	1	0	0	2	0	1	1	5	Satisfactory
Yahya et al. (2021)[8]	1	1	0	2	1	0	1	6	Satisfactory

[a]This table illustrates the assessment quality of cross-sectional studies in this review by using the Newcastle–Ottawa Scale.
[b]Categories of level of evidence: very good, 9-10 points; good, 7-8 points; satisfactory, 5-6 points; unsatisfactory, 0-4 points.

Table 11. Study Quality Assessment Using the Newcastle–Ottawa Scale for Case-Control Studies[a]

Study	Selection				Comparability	Exposure			Quality score, No. of stars.	[b]Level of evidence
	Is the case definition adequate?	Representativeness of the case	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate		
Finkenstedt et al. (1986)[41]	★			★	★	★	★		5	Fair
Pietschmann et al. (1991)[38]	★			★	★★	★	★		6	Fair
Slemenda et al. (1991)[34]	★	★	★	★	★★	★	★		8	Good

[a]This table illustrates the assessment quality of case-control studies in this review by using the Newcastle-Ottawa Scale.
[b]Categories of level of evidence: Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. Fair quality: if there are 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. Poor quality: if there is zero or 1 star in the selection domain OR zero stars in the comparability domain, OR zero or 1 star in the outcome/exposure domain.

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levels of calcium and phosphorus remained within normal ranges in individuals with LI,[36,38,40,42] dietary intake of calcium was consistently lower in this group compared to controls in most studies.[36–38,40–44] In contrast, bone health outcomes were inconsistent across the included studies.[34–40,42–44] Additionally, the overall quality of the included studies ranged from moderate to good, which should be considered when interpreting the consistency of these findings and the general confidence in the conclusions. Some studies reported reduced BMD and BMC in LI,[35,42–44] whereas others found no significant differences compared to lactose-tolerant controls.[34,37,39,40] Findings for bone turnover markers were likewise inconsistent, with a few studies indicating elevated bone resorption,[36,38,42] whereas others reported no notable changes.[37,40]

Heterogeneity in study design, population characteristics, and bone assessment methods appear to be key factors contributing to these discrepancies.

Comparison of Findings With Those of Previous Studies

Micronutrient Status as Measured by Biochemical Micronutrient Status. Across the reviewed studies, no significant differences were observed in serum calcium and phosphorus levels between the LI and control groups, despite reduced dairy intake,[36,38,40,42] in line with Kim et al.,[49] who also reported normal serum calcium and phosphorus levels in young adults with LI.[49]

Normal serum calcium levels may be explained by physiological compensatory mechanisms: reduced dietary calcium triggers secretion of parathyroid hormone (PTH), which increases bone resorption, enhances renal calcium reabsorption, and (via activated vitamin D) promotes intestinal calcium absorption.[50,51] This compensatory response may help explain why serum calcium levels remained largely within the normal range among individuals with LI despite decreased dairy intake.

For phosphate, limited evidence was available; however, our review found that phosphate levels in individuals with LI were normal despite variations in calcium intake and LI status, likely due to compensatory endocrine regulation involving vitamin D, fibroblast growth factor 23 (FGF23), and PTH. Parathyroid hormone enhances renal phosphate excretion, while FGF23 acts in concert to decrease tubular phosphate reabsorption and inhibit 1α-hydroxylase activity, thereby lowering production of active vitamin D (1,25[OH]$_2$D). These coordinated mechanisms maintain calcium balance while preventing hyperphosphatemia. Accordingly, normal phosphate levels in individuals with LI likely reflect efficient physiological adaptation rather than an absence of metabolic disruption. This interaction highlights the integrated roles of phosphate, calcium, and vitamin D in bone health.[50] In addition, as demonstrated in the current study, elevated PTH levels in individuals with LI are a compensatory mechanism for low dietary calcium intake, ensuring serum calcium levels are maintained[52] (Figure 2). However, to prevent reduced BMD and increased risk of osteoporosis over time, adequate calcium and vitamin D intake is critical, as it enhances calcium absorption from the gut, reducing the need for calcium mobilization from the bones and mitigating any detrimental effects.[53]

Regarding vitamin D levels, evidence is limited to 3 studies with inconsistent results. Therefore, we cannot definitively conclude that vitamin D levels are unaffected in individuals with LI. Only 1 study reported insufficient vitamin D in individuals with LI because of dietary restrictions, whereas other studies did not find any significant differences and reported normal values, likely because participants who reduced their intake of dairy products compensated for it with nondairy sources or

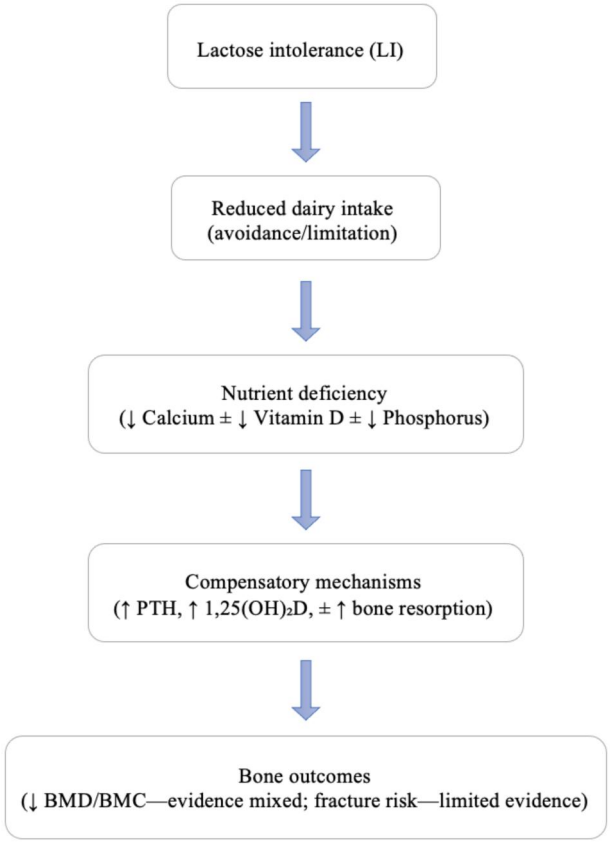

Figure 2. Conceptual Pathway. This figure illustrates the conceptual pathway linking lactose intolerance, reduced dairy intake, nutrient deficiency, compensatory endocrine responses, and bone health outcomes

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; LI, lactose intolerance; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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fortified foods.[54] Another potential reason for normal vitamin D levels could be the elevated PTH levels in LI individuals, which can promote the activation of vitamin D (1,25-dihydroxy vitamin D), thereby masking low total vitamin D levels (25-hydroxyvitamin D).[55] This finding may explain why some studies found normal vitamin D levels even when dietary intake declined. Additionally, individual differences in skin tone and sun exposure may ensure normal vitamin D levels in some individuals. Although the primary source of vitamin D is sunlight, individuals with lighter skin types have lower melanin levels, which tends to allow for more absorption of ultraviolet B rays and produce vitamin D more effectively. In contrast, darker skin types could require more sun exposure to reach the same levels.[56,57] Furthermore, taking supplements or vitamin D–rich foods might increase levels.[57] All of these factors may explain why some people maintain normal vitamin D levels and others do not, even in similar environments.

Although biomarkers provide estimates of actual intake, they have been identified for only a few dietary components thus far, restricting their potential applications. Furthermore, usage of biomarkers is relatively low due to barriers including cost, access to specific analytic expertise and facilities, and the requirement for invasive measures such as blood sampling.[58]

Overall, calcium, vitamin D, and phosphorus are closely interrelated in bone metabolism.[48] Vitamin D plays a critical role in enhancing intestinal calcium absorption, while phosphorus contributes to bone mineralization. As these nutrients are functionally interdependent, deficiency in one may disrupt the balance of others, thereby influencing bone turnover and mineralization. Furthermore, deficiencies in calcium and vitamin D may reduce bone mineral density. At the same time, abnormal phosphorus levels can further impair bone integrity, emphasizing the importance of maintaining balanced levels of these nutrients.

Micronutrient Status as Measured by Dietary Intake. Consistent across studies of varying quality, a general pattern indicates that individuals with LI reported significantly lower calcium intake vs controls due to the avoidance of milk and dairy products.[36–38,40–42,44,45] However, most included studies were observational in design (eg, cross-sectional and case-control), which limits causal inference and may introduce confounding. Nevertheless, the generally good or satisfactory quality of these studies supports the consistency of the observed findings. For instance, Di Stefano et al.[42] reported lower daily calcium intake in LI vs controls, consistent with findings from other pervious evidence.[7,59] This reduction in dairy intake may decrease calcium availability, as dairy products are a primary source of dietary calcium, and consequently impair bone mineralization, providing a possible explanation for the observed associations. Similarly, a recent systematic review associated dairy consumption with higher BMD and lower fracture risk in older adults.[19] Nonetheless, some evidence (eg, Yahya et al.[8]) suggests that individuals with LI can meet their calcium requirements through dietary flexibility, such as consuming nondairy calcium-rich food sources (eg, soybean curd) or taking supplements (calcium, vitamin D, and phosphorus), potentially mitigating deficiencies.

Overall, reduced calcium intake in individuals with LI may increase the risk of suboptimal bone health.[35,42,44] However, further research is needed to confirm this association and account for other contributing factors such as vitamin D status, physical activity, and hormonal influences.

Given that the strength of the evidence remains limited due to the predominance of observational designs and possible residual confounding, these results should be interpreted with caution, as dietary intake data in the included studies may be subject to recall bias and measurement error, especially in studies relying on self-reported dietary questionnaires,[8,35–37,40,41] while others used short-term dietary records,[38,43] which may vary in accuracy. These circumstances may have led to under- or overestimation of nutrient intake. Additionally, discrepancies between self-reported and objectively diagnosed LI may contribute to variability in findings. Possible underreporting may be driven by factors such as recall bias, social desirability bias, and difficulties in estimating portion sizes, particularly among individuals intentionally restricting dairy intake.

Cultural dietary patterns may also influence nutrient intake; for example, populations with traditionally low dairy consumption may rely more on nondairy calcium sources,[60] whereas others may avoid dairy entirely due to perceived intolerance,[6] contributing to variability in reported intake.

Bone Health. Most studies reported no significant differences in BMD between normal individuals and those with LI, with most studies being of good or satisfactory quality,[8,34,37,39,40,43] which increases confidence in the overall findings although the observational nature of these studies still limits causal inference. These findings may reflect mild-to-moderate reductions in calcium intake and/or partial compensation through other dietary sources that were insufficient to produce measurable BMD changes. This observation may be partly explained by compensatory behaviors: for example, Enattah et al.[61] found that women with LI who frequently used calcium supplements did not have low bone density, and some individuals may tolerate small amounts of milk (a dose of at least 12 g lactose) without symptoms and therefore do not avoid milk completely.[62] Conversely, other good or satisfactory quality studies reported[35,42,44] significantly

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lower BMD in individuals with LI, particularly at the lumbar spine and other skeletal sites indicating compromised bone strength that may have been related to long-term lower calcium intake.[35,42,44] This finding is consistent with evidence suggesting that dairy avoidance may negatively affect BMD and fracture risk.[19] For example, a 16-month milk-provision program showed that calcium intake increased from 55% to 85% of the recommended level, and the decline in T-score in the lactose-intolerant group was significantly smaller than in controls.[63]

Similarly, BMC measures the overall mineral accumulation in bone and its reduction. Findings were mixed: 1 study reported no significant BMC difference,[40] whereas others found lower (or significantly lower) BMC in LI vs controls.[42,43] The quality of these studies ranged from good to acceptable, which may partly explain the variability in findings. Disparities likely reflect differences in menopausal status, diet, physical activity (particularly weight-bearing exercise that enhances BMD), and variation in BMC measurement methods (eg, dual-energy X-ray absorptiometry, quantitative computed tomography).[40,42,43]

The comparability and interpretation of BMD/BMC results may be affected by methodological heterogeneity across studies. Variations in imaging modalities (eg, DEXA, QC, and photon absorptiometry), each with different sensitivities and measurement principles. For instance, Horowitz et al.[37] used photon absorptiometry and vertebral densitometry, whereas Di Stefano et al.[42] used DEXA-based assessments, which may partly explain inconsistencies in reported outcomes. In addition, site-specific differences in BMD measurements (eg, spine vs hip) may contribute to variability in reported outcomes.[35,43] Differences in population characteristics (eg, BMI, physical activity, and menopausal status) may act as confounding factors if not adequately adjusted for, thereby influencing observed associations. Furthermore, several studies,[36,38,44] including those by Pietschmann et al.,[38] had relatively small sample sizes, which may have reduced statistical power and limited the detection of significant associations. Together, these methodological differences should be considered when interpreting the overall relationship between LI and bone health outcomes.

Decreased milk intake negatively affects bone health, highlighting the importance of dietary calcium in maintaining bone health.[7,19] Moreover, LI has been associated with alterations in bone remodeling and mineralization.[36,38,42] Delayed mineralization yields softer, weaker bone reflected by increased osteoid volume and seam width.[36] Elevated tetracycline labeling (%) indicates active bone formation as a compensatory response, albeit inefficient.[36] Higher levels of the carboxy-terminal telopeptide of type I collagen (μg/L) and increased osteocalcin suggest excess resorption, further weakening bones and increasing fracture risk of fractures.[38,42] Balanced mineralization and turnover are therefore essential to preserve bone strength.

Bone turnover markers can provide additional information for evaluating bone health by reflecting early changes in bone metabolism that BMD may not yet be able to detect. However, the interpretation of such information is influenced by assay variability, measurement timing, and differences in analytical methods across studies. For example, included studies used different approaches to assess bone metabolism, such as serum osteocalcin measurements and histomorphometric analyses, which assess different aspects of bone formation and turnover.[36,38] In addition, bone density measurements were performed using different techniques, including DEXA, QCT, and photon absorptiometry, each with different levels of precision and comparability.[37,40] While BMD measurements are generally precise, variability in methods and lack of standardization across studies may limit direct comparisons.

In clinical settings, these markers may complement BMD in evaluating fracture risk; however, evidence from the included studies suggests that they are more reflective of short-term metabolic changes rather than consistent predictors of long-term bone outcomes.[42]

The observed associations may have been affected by diagnostic method variability, including differences in the accuracy of HBT and LTT, as well as possible misclassification and variations in LI phenotypes (primary vs secondary). This variability could have led to inconsistent results in nutrient intake and bone outcomes across studies and may result in misclassification of LI status, which can affect estimates of nutrient intake and make the association with bone health outcomes potentially biased and less clear. Overall, heterogeneity appears multifactorial, reflecting variations in study design, population characteristics (especially age and menopausal status), and bone assessment methods; no single factor consistently explained the variability, and subgroup analyses did not completely account for these discrepancies. These results help explain the variability in BMD findings across studies. This is consistent with Falbová et al.,[64] who reported BMD as a multifactorial trait influenced by genetics, age, physical activity, calcium intake, lifestyle, and hormonal status.[64]

This review also included studies in postmenopausal women and those with osteoporosis, given their increased risk of bone health issues. For instance, Callegari et al.[43] and Corazza et al.[44] found that postmenopausal women with LI and those with osteoporosis had lower BMD and BMC than controls and experienced an exacerbation of osteoporosis. Vigorita et al.[36] proposed that persistent bone formation at sites of successful calcification may contribute to osteoporotic bone loss. Our findings align with prior work reporting decreased BMD in postmenopausal women with LI.[65] Other previous studies showed a higher incidence of lactase deficiency in women with osteoporosis vs those without.[66,67] This

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finding suggests that lactase deficiency may predispose individuals to osteoporosis by reducing milk intake due to LI or by impairing calcium absorption. A higher occurrence of fractures associated with reduced BMD and chronic calcium inadequacy has been observed in individuals with severe LI.[40] Further research on fracture outcomes in this population is needed.

Given the increased risk observed in specific subgroups, particularly individuals with osteoporosis and postmenopausal women, clinical care should focus on ensuring adequate calcium and vitamin D intake through individualized dietary planning, including the use of lactose-free or fortified alternatives. Additionally, targeted screening may help guide appropriate intervention. In particular, calcium inadequacy, with intake often below recommended levels, is related to reduced dairy intake and may be addressed through lactose-free or fortified alternatives, whereas vitamin D deficiency may require targeted supplementation or the use of fortified foods due to limited dietary sources. These findings highlight the probability that dietary strategies may be sufficient in some cases, whereas supplementation may be necessary in others depending on the degree of inadequacy.

Strengths, Limitations, and Future Research Recommendations

This study has several strengths: First, a systematic approach was used with defined searches across multiple data sources and strict inclusion criteria, including physiologically confirmed LI, which improved reliability. Second, misclassification was minimized by excluding studies that relied on self-reported LI and included those using objective diagnostics. Third, this review incorporated phosphorus results, a parameter seldom examined in prior reviews. Fourth, the evidence was updated through 2024, enhancing the relevance and currency of the findings.

Limitations of this study include the predominance of cross-sectional designs, which limit causal inference, and relatively small sample sizes. Several included studies demonstrated limited or inconsistent adjustment for key confounders (eg, BMI, physical activity, sun exposure, ethnicity, dietary patterns, and supplement use), which could affect the interpretation of the results. In addition, potential publication bias and the limited availability of longitudinal studies should be considered. Additional methodological limitations include variability in vitamin D measurement methods. For example, 1 study[37] used a competitive protein-binding assay, whereas others[35,42] used serum/blood-based measurements, resulting in variability in reported vitamin D status.

The scarce fracture outcomes across studies, together with variability in samples and reported outcomes. Geographic under-representation (eg, Middle East and Africa) was also noted. Prospective cohorts or intervention trials, and inclusion of under-represented regions, are needed to clarify associations between LI, lower nutrient intake, and bone outcomes, and to evaluate effective dietary strategies. Future work should also extend beyond calcium, phosphorus, and vitamin D to consider other bone-relevant nutrients, (eg, magnesium, potassium, and vitamin B12). Addressing these gaps is essential for culturally appropriate, evidence-based dietary interventions to improve bone health and overall well-being in this population.

CONCLUSIONS

This systematic review indicates that although serum calcium and phosphorus frequently remain within reference ranges in individuals with LI, calcium intake is commonly reduced due to dairy avoidance. Although serum calcium and phosphorus levels often remain within normal ranges, this finding may reflect physiological or dietary compensatory mechanisms (eg, PTH- and vitamin D-related regulation) that help maintain normal serum levels despite reduced intake, but may not be sufficient to preserve optimal bone health over time. Evidence regarding vitamin D status in LI is particularly limited and insufficient for reaching conclusions, while evidence regarding phosphorus also remains limited, with few studies directly assessing its role in bone health among individuals with LI. Associations between LI and bone outcomes (BMD/BMC, osteoporosis) are mixed across studies and do not permit causal inference; observed findings in specific subgroups (eg, postmenopausal women) are also inconsistent. Only 1 study specifically assessed fracture incidence.[40] This is further limited by the observational nature of the included studies, which are subject to remaining confounding, as well as by heterogeneity across populations, study designs, and measurement methods. Together, these findings suggest that reduced intake of key bone nutrients, particularly calcium due to dairy avoidance may trigger compensatory physiological mechanisms that help maintain serum levels, but these adaptations may not fully protect long-term bone outcomes.

From a clinical perspective, given these uncertainties, clinical care should focus on ensuring adequate calcium and vitamin D through individualized dietary planning, including the use of lactose-free or fortified alternatives, appropriate screening where indicated, and supplementation, rather than assuming a uniformly adverse effect of LI on bone health. Future research should employ prospective cohort designs, including underrepresented populations identified in this review, particularly from non-European regions such as the Middle East and Africa. Studies should incorporate comprehensive nutrient assessments, extending beyond calcium and vitamin D to include other bone-relevant micronutrients such as phosphorus and magnesium. In addition,

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the use of standardized diagnostic and assessment methods is recommended, alongside studies evaluating fracture outcomes to clarify the long-term impact of LI on bone health and inform targeted nutritional strategies. Overall, while LI does not appear to consistently impair bone health, reduced intake of key nutrients, alongside variability in the evidence, highlights the importance of individualized clinical management and provides important insights into bone health mechanisms, while identifying key gaps in current scientific research.

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Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

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Conflicts of Interest

None declared.

Data Availability

All data relevant to the review are included in the article and its supplementary material.

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