



## Narrative Review

## Factors influencing adherence to dietary management in patients with classical galactosemia: A systematic review



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## ABSTRACT

Lifelong dietary restriction is the main approach to managing classical galactosemia, yet maintaining adherence is challenging and poorly understood. Existing research has focused primarily on metabolic outcomes, with limited synthesis of the behavioral, psychosocial, and healthcare system factors shaping long-term dietary management. This systematic review aimed to identify determinants of dietary adherence in individuals with classical galactosemia and to synthesize these factors using the socio-ecological model to provide a multi-level understanding of influences on adherence.

A systematic search of PubMed, Scopus, Web of Science, and Embase was conducted following PRISMA guidelines. Studies examining factors related to dietary management in classical galactosemia were included. Extracted determinants were synthesized narratively and deductively mapped to individual, interpersonal, healthcare system, community, and structural levels of the socio-ecological framework. Study quality was assessed using the JBI critical appraisal tool.

Evidence directly examining adherence determinants was limited. However, psychosocial and contextual findings revealed consistent multi-level influences. Individual factors included psychological burden and cognitive challenges; interpersonal influences involved caregiver involvement and family dynamics; healthcare-level determinants related to access to specialist metabolic care and variability in dietary guidance; community factors included barriers to social participation; and structural concerns reflected long-term dependency and support needs. These findings suggest that dietary adherence in classical galactosemia is shaped by interacting ecological influences rather than solely individual behavior. Addressing psychosocial burden, family support, healthcare system consistency, and social participation barriers may be critical for improving long-term dietary management. The scarcity of adherence-focused research highlights the need for theory-informed, multi-level intervention studies in this rare metabolic disorder.

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## 1. Introduction

Inborn errors of metabolism (IEMs) are a diverse group of genetic disorders caused by defects in metabolic pathways, often leading to the accumulation of toxic substances or deficiency of essential metabolites [1]. In 1902, Sir Archibald Garrod reported

the first description of an inborn error of metabolism [2]. Since then, over 1000 well-characterized IEMs have been identified, with ongoing updates as new disorders are discovered [3]. IEMs have an overall incidence of more than 1:1000, although being infrequent when developed separately [4]. IEMs are typically classified by the affected metabolic pathway or molecule, such as amino acids, organic acids, fatty acids, carbohydrates, and metals [5].

Classic galactosemia (CG), an inborn error of metabolism, is an autosomal recessive disorder of carbohydrate metabolism caused

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by a severe deficiency of the enzyme galactose-1-phosphate uridylyltransferase (GALT), which is accountable for converting galactose-1-phosphate and uridine diphosphate glucose (UDP-glucose) into uridine diphosphate galactose (UDP-galactose) and glucose-1-phosphate [6]. The accumulation of galactose metabolites and a deficiency of UDP-hexoses occur as an outcome of profoundly reduced GALT activity [7]. Protein structural disorder, which leads to a significant loss of GALT activity, has identified CG as a conformational disorder, with the buildup of its substrate Gal-1-P reliably recognized as a major pathogenic factor [8]. In addition to life-threatening complications at neonatal period, individuals with classical galactosemia may also experience long-term complications such as lower growth, speech difficulties, cataracts learning and cognitive delays, movement issues like ataxia, and in females, early ovarian failure or hormonal imbalances, etc. [9].

Dietary intervention is recommended as a primary treatment upon suspicion of classical galactosemia [10]. Dietary elimination of galactose can prevent or reverse the acute manifestations of CG [11]. A proposed contributor to the variability in long-term outcomes of classical galactosemia is how strictly dietary galactose is limited during early development. As knowledge of galactose in non-dairy foods has improved, dietary management for children with classical galactosemia has been revised accordingly [12].

Considerable dispute still remains about how severe and how long dietary galactose restriction should be, although its long-standing background. Despite the importance of a galactose-restricted diet, there's a significant gap in how diet is managed in adults, and dietetic follow-up is often not maintained [13]. While adhering to the diet was difficult, living with galactosemia was yet considered as 'very good' or 'good' [14]. However, maintaining dietary adherence is influenced by numerous interconnected factors including family involvement, social support, economic conditions, the healthcare providers, etc. [15].

Although dietary restriction is the central management strategy for classical galactosemia, evidence on what drives or hinders adherence remains limited and scattered across small, heterogeneous studies. While dietary restriction is the cornerstone of management in classical galactosemia, research has predominantly focused on biochemical outcomes and metabolic control. The behavioral, psychosocial, and healthcare system determinants that shape long-term dietary adherence remain poorly conceptualized. No prior synthesis has examined adherence through a theoretical behavioral framework, limiting the development of targeted interventions.

To date, no review has synthesized dietary adherence determinants in classical galactosemia using a behavioral theory framework. Therefore, this systematic review aims to synthesize existing evidence on the factors influencing adherence to a galactose-restricted diet in individuals with classical galactosemia. By identifying key barriers and facilitators, this review seeks to provide actionable insights that can guide clinical practice, strengthen follow-up strategies, and support evidence-based dietary interventions.

## 2. Method

### 2.1. Registration protocols

This systematic review followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. The review protocol was registered in the International Prospective Register of Systematic Reviews under the registration ID CRD420251050899 [17].

### 2.2. Eligibility criteria

#### 2.2.1. Inclusion criteria

1. Population: Patients of any age with a confirmed diagnosis of classical galactosemia.
2. Intervention/Exposure: Dietary management strategies aimed at restricting or modifying galactose intake.
3. Outcomes: Studies that reported on adherence to dietary management and factors influencing adherence, including clinical, psychosocial, behavioral, cultural, or caregivers.
4. Language and publication date: Articles published in English, with no restriction on publication year.
5. Study designs considered: Qualitative, cross-sectional, case-control, correlational, cohort, randomized controlled trials, and mixed-methods studies published in full text were included.

#### 2.2.2. Exclusion criteria

1. Did not focus on classical galactosemia.
2. Reported only biochemical or clinical outcomes without assessing adherence.
3. Systematic reviews, meta-analyses, literature or narrative reviews, scoping reviews, umbrella reviews, editorials, letters, commentaries, and articles available only as abstracts.

### 2.3. Search engines/databases

A comprehensive literature search was conducted using the Global Health, MEDLINE, Web of Science, PubMed, Scopus, and ProQuest Dissertations and Theses databases to identify relevant studies. No restrictions were placed on the publication date, allowing for the inclusion of all potentially relevant literature regardless of the time of publication. To enhance the thoroughness of the search and minimize the risk of omitting pertinent studies, additional strategies were employed. This included citation tracking of included studies, reference list screening of relevant articles, consulting experts or corresponding authors, and supplementary searches using Google Scholar.

### 2.4. Search strategy

Two authors (MMH and UD) independently conducted systematic searches across several Databases. The search utilized keywords, incorporating medical subject headings in boolean operators. The initial search was conducted on March 23, 2025, with an updated search of all databases on August 29, 2025. Full search terms for PubMed are provided in the [Supplementary Table 1](#).

### 2.5. Selection criteria

After eliminating duplicate records, two members of the research team (NSN, AD, FA, TS, NNR, PC, MA) independently screened each title and abstract obtained from the search based on predefined inclusion and exclusion criteria. In cases of disagreement during abstract screening, a third reviewer (MMH, AR, or UD) determined whether the study met the inclusion criteria. Each full-text article was independently evaluated for eligibility by two members of the project team (NSN, AD, FA, NNR, PC, MA, TS). Reasons for exclusion were recorded during this stage. Data from

the eligible studies were then extracted (MMH, UD, MABH) using a pre-designed and pilot-tested template developed by the authors. Any disagreements concerning study eligibility or data extraction were resolved through discussion, with the involvement of a third reviewer (AR) when required. The screening process was conducted using Rayyan [18] to ensure a systematic and efficient selection of studies.

## 2.6. Theoretical framework and analytical approach

The socio-ecological model by U Bronfenbrenner [19] was used as an interpretive framework to categorize and synthesize factors influencing dietary adherence at multiple levels, including individual, interpersonal, healthcare system, community, and policy contexts. Identified determinants from included studies were deductively mapped using a directed content analysis approach to these levels during data synthesis to facilitate theory-informed interpretation.

## 2.7. Data synthesis

Studies addressing adherence to dietary management in patients with classical galactosemia were systematically compiled and described. The extracted findings were synthesized and organized according to the specific factors reported to influence dietary adherence. A narrative synthesis approach was employed to identify, group, and summarize determinants of dietary adherence across included studies, followed by theory-informed categorization using the socio-ecological model.

## 2.8. Risk of bias assessment

The Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data was used as the quality assessment tool. Each study was assessed independently by two reviewers of project members (UD, MMH and MABH), and any disagreements were resolved through discussion. A third reviewer (AR) was available to mediate when necessary. Each study was evaluated based on the nine JBI items and assigned a score ranging from one to nine. These scores were then converted into percentages to classify the level of bias as follows: 49 % and lower as high risk of bias, 50–69 % as moderate risk of bias, and 70 % and above as low risk of bias [20]. Importantly, no studies were excluded based on their quality rating in order to maintain transparency and ensure that all available evidence within this field was captured and reported.

## 3. Result

### 3.1. Study selection

A total of 1233 articles were identified through database searches, including Global Health, MEDLINE, Web of Science, PubMed, Scopus, and ProQuest Dissertations and Theses. An additional 35 records were identified through manual searches of Google Scholar and reference lists. After removing 639 duplicates, 629 articles remained for title and abstract screening. Following screening, 600 articles were excluded based on title and abstract. The full text of 29 articles was retrieved for further assessment. Of these, 24 articles were excluded (Supplementary Table 2) after full-text evaluation due to following reasons: 5 articles had wrong study design, 8 articles had wrong outcome and 11 articles did not discuss any factors related to adherence. In total, 5 articles were included in this systematic review. The selection process is

summarized in a flow diagram, according to PRISMA guideline, provided in Fig. 1.

### 3.2. Study overview

The five studies included in this review were conducted across diverse geographical regions, including the United Kingdom, Germany, Australia, and multiple international cohorts spanning Europe, Australia, and other continents. All studies adopted a cross-sectional design. Sample sizes varied considerably, ranging from 13 patients in the smallest study to 418 patients in the largest international survey. Participants represented a wide age spectrum, from infants and children under 18 years to adults up to 49 years of age. In some cases, caregivers and healthcare professionals were surveyed to provide insights into adherence-related challenges and practices. The populations included were individuals diagnosed with classical galactosemia and maintained on a galactose-restricted diet. Dietary adherence was assessed predominantly through self-reported questionnaires, with some studies employing validated instruments such as the Quality-of-Life Profile for the Chronically Ill (PLC), while others relied on non-validated or proprietary questionnaires. In one study, dietary adherence was reported by healthcare professionals based on clinical follow-up and diagnostic tests. Table 1 provides the overview of studies included in this systematic review.

### 3.3. Quality and risk of bias assessment

The methodological quality of the included studies, assessed using the JBI critical appraisal checklist, showed considerable variation. Quality scores ranged from 37.5 % to 75 % across the five studies. One study [21] achieved a high-quality rating ( $\geq 70$  %), indicating a low risk of bias. Two studies [11,14] were classified as having a moderate risk of bias, with quality scores between 50 % and 69 %. The remaining two studies [22,23] demonstrated lower methodological quality, scoring  $\leq 49$  %, and were therefore considered at high risk of bias.

### 3.4. Factors affecting dietary adherence

This review identified several categories of factors that influence dietary adherence among patients with classical galactosemia. These were grouped into three key themes. Social, cultural and emotional influences; caregiver-related factors; nutritional considerations; and the attitudes of healthcare professionals. The findings are summarized in Table 2.

#### 3.4.1. Psychosocial, cultural and emotional factors

Three studies demonstrated social [11,14,23], cultural [11], and emotional [23] factors affecting adherence to diet in patients diagnosed with classical galactosemia. One study [14] found that while a majority of adult patients reported no or only partial burden in following the diet, those who did perceive it as burdensome showed significantly higher negative mood and lower scores in positive mood, social well-being, and social functioning ( $p < 0.05$  for all correlations).

Cultural dietary patterns and social stigma emerge as substantial barriers to adherence, particularly as patients mature. Study indicated a tendency for dietary adherence to diminish with increasing age. Cultural reliance on certain foods and social stigma have been cited as contributing factors to this decline [11].

Patients explicitly recognize the social and emotional discomfort resulting from food restrictions as a major source of distress, which directly affects their ability to adhere to the diet. Disruptions to social norms and food-related personal identities are

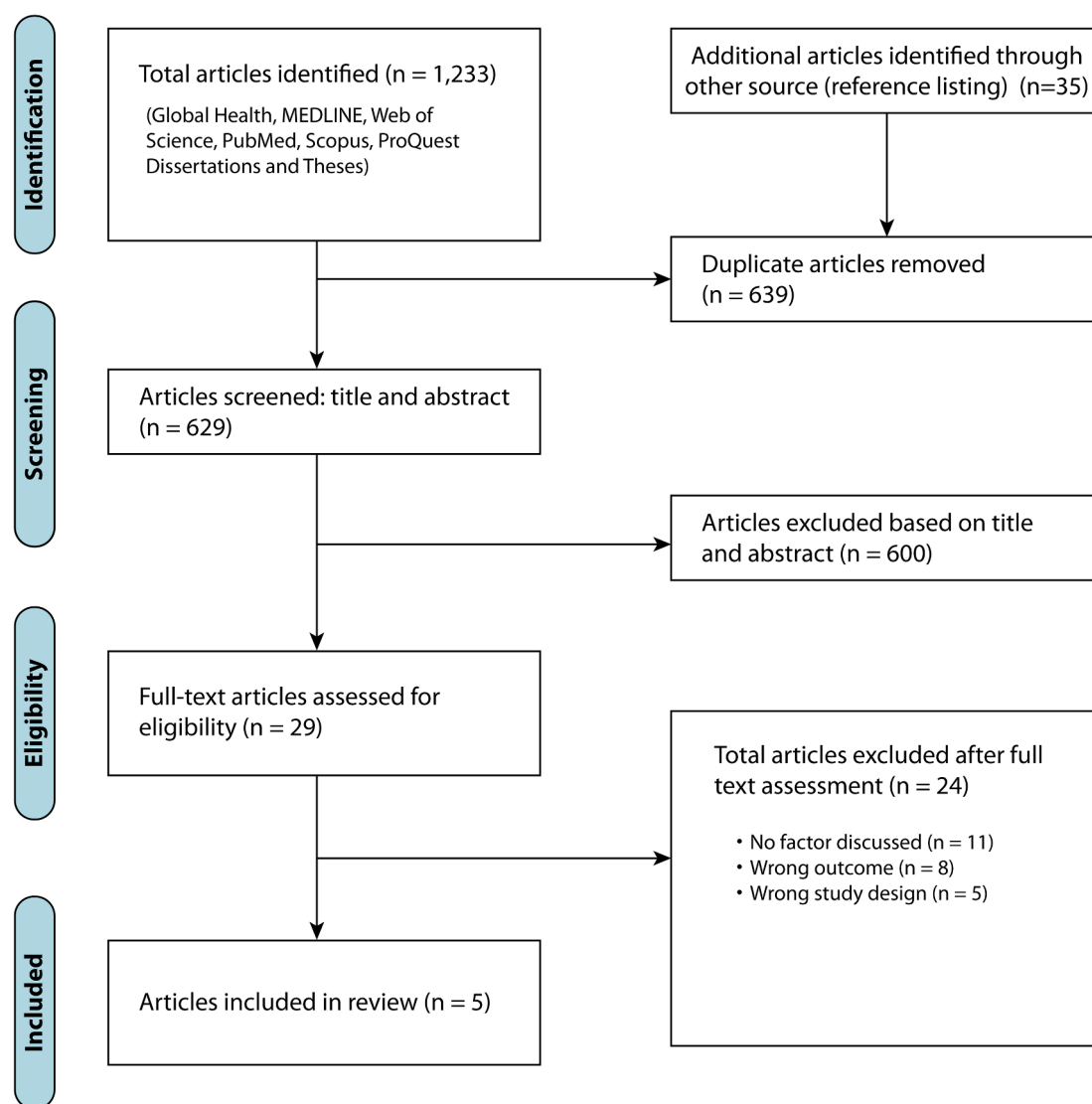


Fig. 1. PRISMA reported flowchart for study selection process.

included in this discomfort, which goes beyond simple food avoidance. For instance, navigating social gatherings or shared meals can become a source of anxiety or isolation when dietary options are severely limited. Patients reported feeling “different from others” and experiencing social isolation, with some noting they “just had no friends.” This feeling of being set apart was also reflected in patients' perceptions that their parents treated them differently from their siblings, a perception not shared by the parents themselves. This challenge is further exacerbated by experiences of bullying, which a notable proportion of patients reported, often linked to perceived differences or expressions of anger [23].

### 3.4.2. Caregiver related factors

Caregivers play an important role in managing the therapeutic diet for patients with Galactosemia, especially for newborns and young children whose compliance is completely dependent on them. A study [21] surveyed caregivers of children with Galactosemia in the UK, provided detailed insights into the factors that support or challenge their ability to maintain the diet. The study revealed that the majority of caregivers demonstrated a high level

of nutrition-related knowledge regarding the Galactosemia diet. Nearly all participants (98 %) were classified as having a high level of knowledge, and a significant positive correlation ( $p = 0.013$ ) was found between higher education levels and higher knowledge scores. In terms of perceptions, the overall attitude toward the diet was positive, with 65 % of caregivers achieving high attitudinal scores. However, almost half of the caregivers (49 %) held negative perceptions about being unable to feed their child breast milk.

Despite this high level of knowledge and positive attitude, caregivers reported numerous practical and emotional barriers to adhering to the diet. 79 % of caregivers expressed concerns about the safety of their child in social settings, and 53 % found social events involving eating out to be stressful. Significantly, 49 % of caregivers believed their child's diet excluded them from social situations. The study identified other common barriers, including the high cost of groceries (53 %) and fears for their child's health (44 %). Furthermore, a significant association was found between a child's age and caregiver concerns about the diet being time-consuming and expensive ( $p = 0.090$  and  $p = 0.048$ , respectively). A key finding was that caregivers often faced multiple barriers simultaneously, with the majority reporting at least four

**Table 1**

An overview of included studies in this review.

| Author                      | country                                                                                                                     | Study Design          | Sample Size (n)                    | Age Group (sex)                              | Study period            | Population Description                                                                                                                                                                                                                            | Dietary Adherence Measure | Assessment Tools                                                                                                                            |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------|----------------------------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Blaauw, Dolman-Macleod [21] | United Kingdom                                                                                                              | Cross-sectional study | 43 caregivers                      | Not mentioned                                | April 2022 to July 2022 | Primary caregivers of infants and children (birth to under 18 years) diagnosed with classical galactosaemia, following a galactose-restricted therapeutic diet, and residing in the UK                                                            | Self-reported             | Online questionnaire                                                                                                                        |
| Hoffmann, Dragano [14]      | Germany                                                                                                                     | Cross-sectional study | 41 patients                        | Mean age: 26.2 ± 7.2 years (range 18.3–49.3) | Not mentioned           | Adult patients with CG, confirmed GALT-deficiency (<5 % compared to healthy controls), members of the German galactosemia patient support group                                                                                                   | Self-reported             | Proprietary non-validated questionnaire (disease-specific information), quality of life profile for the chronically ill (PLC) questionnaire |
| Adam, Akroyd [22]           | 12 countries (UK, Germany, Netherlands, Belgium, Australia, France, Italy, Spain, Sweden, New Zealand, Norway, Switzerland) | Cross-sectional study | 418 patients                       | Not mentioned                                | Not mentioned           | Adults with classical galactosaemia attending 39 European and Australasian international IMD centers                                                                                                                                              | Self-reported             | Questionnaire                                                                                                                               |
| Jumbo-Lucioni, Garber [11]  | 11 countries (Argentina, Croatia, Germany, Italy, Mexico, Netherlands, Philippines, South Africa, Spain, UK, USA)           | Cross-sectional study | 13 health care professionals       | Not mentioned                                | 2007 and 2008           | 234 patients with CG under the care of metabolic specialists, pediatric endocrinologists, or geneticists; representing diverse ethnic backgrounds: Caucasian (n = 191), Hispanic (n = 29), African American (n = 5), Asian (n = 1), Asian (n = 8) | Reported by providers     | Clinical follow-up (diagnostic tests)                                                                                                       |
| Lambert and Boneh [23]      | Australia                                                                                                                   | Cross-sectional study | 13 patients; 12 individual parents | Age range 6–23 years; females 8, males 5     | 2002–2003               | Patients with galactosaemia who attend the metabolic unit outpatient clinic, royal Children's Hospital, Melbourne. all participants were treated with a galactose-restricted diet                                                                 | Self-reported             | Questionnaire                                                                                                                               |



**Table 2**

An overview of studies investigating the influence of factors on dietary compliance.

| Author                      | Participants              | Factors                                                    | Main Findings                                                                                                                                                                                                                                                                                                           |
|-----------------------------|---------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blaauw, Dolman-Macleod [21] | Caregivers                | Caregivers' knowledge, perceptions, practices and barriers | High caregiver knowledge, along with positive attitudes and strong confidence in diet management, supported adherence, while reported barriers challenged adherence; all children were reported to follow a dairy-free diet.                                                                                            |
| Hoffmann, Dragano [14]      | Patients                  | Psychosocial                                               | The majority of patients reported no or only partial burden in following the diet; however, those perceiving the diet as burdensome showed significantly higher negative mood ( $p = 0.43$ ) and lower scores in positive mood ( $p = 0.44$ ), social well-being ( $p = 0.41$ ), and social functioning ( $p = 0.34$ ). |
| Adam, Akroyd [22]           | Patients                  | Health professionals' attitude                             | Low dietary adherence was correlated with less conviction among dietitians about the necessity of strict dietary restrictions.                                                                                                                                                                                          |
| Jumbo-Lucioni, Garber [11]  | Health care professionals | Cultural and social factors                                | Dietary adherence reduced with age; cultural dietary patterns and social stigma was mentioned as barriers in dietary adherence                                                                                                                                                                                          |
| Lambert and Boneh [23]      | Patients and parents      | Social and emotional factors                               | Patients recognized the social and emotional discomfort of food restrictions as a major source of distress, which could affect adherence.                                                                                                                                                                               |

or more different types of challenges to their child's adherence to the galactosemic diet.

### 3.4.3. Role of healthcare professionals

The attitudes and conviction levels of healthcare professionals, particularly dietitians, play a critical role in influencing patient adherence to diet. An international survey of dietetic practices [22], revealed a degree of uncertainty among professionals regarding the necessity of a strict diet for adults with galactosemia. Even though a rigorous diet was considered necessary by more than 75 % of the centers surveyed, there was a clear association between lower patient dietary adherence and a lack of conviction among health professionals about the need for rigorous dietary restrictions. The study also revealed a notable disconnection between professional guidance and patient behavior. It was observed that while diets were relaxed in 38 % of the centers, this was more often "mainly self-directed by patients than dietitians.

## 3.5. Socio-ecological determinants influencing dietary management

Across the five included studies, a range of factors relevant to dietary adherence in classical galactosemia were identified and mapped onto the socio-ecological model, spanning individual, interpersonal, healthcare system, and community/structural levels. The findings are summarized in Table 3.

### 3.5.1. Individual-level factors

At the individual level, psychological and quality-of-life-related factors were consistently reported. Caregivers described the therapeutic diet as burdensome and emotionally demanding, with fear of dietary errors and long-term consequences contributing to psychological strain. Although caregivers generally demonstrated adequate nutrition-related knowledge, negative illness perceptions and emotional responses persisted [21]. Both adults and adolescents identified dietary restrictions as a major challenge affecting daily life, with reductions in health-related quality of life, particularly in social and emotional domains, highlighting potential implications for long-term adherence to dietary management. In addition, functional limitations affecting independent living and daily self-management were described in adult populations, which may influence autonomy in disease and dietary management [14,23].

### 3.5.2. Interpersonal-level factors

Interpersonal determinants primarily related to family dynamics and social participation. Dietary management during childhood was largely caregiver-driven [21], and a substantial proportion of adults continued to live with parents [14]. Families reported emotional stress associated with ongoing dietary management and concerns about long-term outcomes [21]. Social participation constraints were also evident, with lower social functioning and difficulties engaging in shared meals and social eating situations reported, highlighting interpersonal contexts that may complicate dietary management [14,23].

### 3.5.3. Healthcare system-level factors

At the healthcare system level, considerable variation was observed in dietary recommendations, restriction strictness, and monitoring practices across countries and clinical settings [11,22]. This heterogeneity contributed to uncertainty among patients and caregivers regarding optimal dietary management. Several studies emphasized that dietary treatment alone was insufficient and highlighted the importance of specialized, multidisciplinary follow-up addressing medical, dietary, and psychosocial needs across the lifespan [11,14,21]. Limited continuity of care into adulthood was also reported, with variability in adult follow-up and monitoring following transition from pediatric services [11,14]. The distribution of these healthcare-related determinants within the broader socio-ecological framework is illustrated in Fig. 2.

### 3.5.4. Community and structural factors

Community and structural determinants included employment, economic, and cultural contexts. Adults with classical galactosemia experienced high rates of unemployment and incomplete vocational participation, representing potential structural barriers that may indirectly affect long-term dietary management [14]. Caregivers reported increasing financial concerns related to maintaining the therapeutic diet over time [21]. Additionally, cultural and societal food environments, particularly dairy-centered dietary norms and differing national food practices, were identified as contextual factors complicating adherence to galactose-restricted diets [11,22].

**Table 3**

Mapping of factors influencing dietary adherence in classical galactosemia using the socio-ecological model.

| Determinant                                                     | Conceptual Interpretation                                                                                                                                                                                                                                                 | Quantitative Findings (n/N, %)                                                                                                                                                                 | SEM level            |
|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Psychological burden of dietary restriction                     | Caregivers described the therapeutic diet may be burdensome and emotionally demanding, with fear of mistakes and long-term consequences contributing to psychological strain [21]. Adults reported dietary restrictions as one of the most affected life domains [14,23]. | Adults reported diet as partly burdensome 36.6 % (15/41) and absolutely burdensome 4.9 % (2/41); 58.5 % (24/41) reported no burden [14].                                                       | Individual           |
| Health-related quality of life (HRQoL)                          | Reduced HRQoL was reported among adolescents and adults, particularly in social and emotional domains [14,23].                                                                                                                                                            | Adults reported that galactosemia impaired company with others: 9.8 % absolutely (4/41), 29.3 % partly (12/41) in [14]; 61.5 % (8/13) reported difficulty 'getting along with others' in [23]. | Individual           |
| Cognitive and emotional limitations affecting self-management   | Adults exhibited emotional limitations affecting independent living and daily management, potentially limiting autonomous disease and dietary self-management [14,23].                                                                                                    | 30.8 % (4/13) reported 'really mad very often'; 30.8 % (4/13) reported 'really mad sometimes.' [23]                                                                                            | Individual           |
| Nutrition-related knowledge and illness perceptions             | While caregivers generally demonstrated good dietary knowledge, negative perceptions persisted [21].                                                                                                                                                                      | 53 % (23/43) reported caregivers reported stress related to eating out [21].                                                                                                                   | Individual           |
| Dependence on parents/caregivers for dietary management         | Dietary management in childhood relied heavily on caregivers, and more than half of adult patients continued to live with parents [14,21].                                                                                                                                | 79 % (34/43) caregivers expressed concern about safety in social setting of the children [21].                                                                                                 | Interpersonal        |
| Emotional burden                                                | Caregivers reported emotional stress related to daily dietary management and concern over long-term outcomes, potentially affecting consistency of adherence support [21].                                                                                                | 44 % (19/43) caregivers reported fears regarding child's health; more than 4 concurrent barriers reported by 21 % (9/43) caregivers [21].                                                      | Interpersonal        |
| Social participation constraints in eating contexts             | Lower social functioning and difficulties participating in shared meals were reported [14,23].                                                                                                                                                                            | 21 % (9/43) caregivers believed child's diet excluded them socially [21].                                                                                                                      | Interpersonal        |
| Variation in dietary recommendations and restriction strictness | Marked international variation was observed in diagnostic approaches, dietary restriction practices, and monitoring, leading to uncertainty for patients and caregivers regarding optimal adherence [11,22].                                                              | 92 % (12/13) providers recommended indefinite restriction; 30.8 % (4/13) reported relaxation of restrictions in older patients [11].                                                           | Healthcare system    |
| Need for specialized and multidisciplinary follow-up            | Studies emphasized that dietary treatment alone is insufficient and highlighted the importance of structured follow-up addressing medical, dietary, and psychosocial needs across the lifespan [11,14,21].                                                                | 32 % of patients reported lost to follow-up in international practice survey [22].                                                                                                             | Healthcare system    |
| Employment and occupational challenges                          | High rates of unemployment and incomplete vocational participation were reported [14].                                                                                                                                                                                    | 24.2 % of adults (8/33) were not employed [14].                                                                                                                                                | Community/Structural |
| Financial burden of specialized diets                           | Caregivers reported increasing concern about food costs associated with maintaining the therapeutic diet over time, representing an economic barrier to sustained adherence [14,21].                                                                                      | 53 % (23/43) caregivers concerned about grocery cost [21]; adults reported mean extra €145/month (range €0–400) [14].                                                                          | Community/Structural |

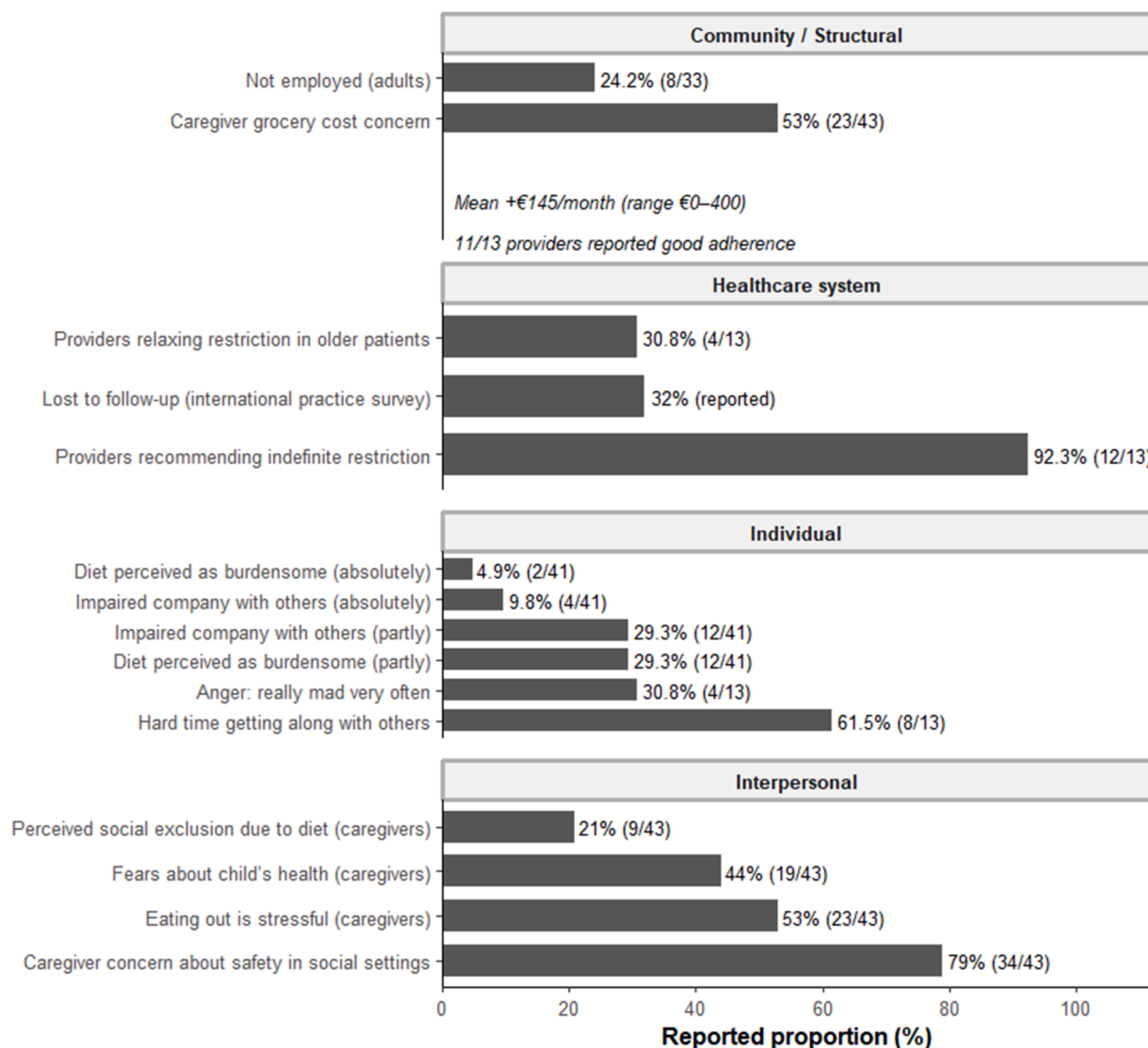
#### 4. Discussion

This systematic review examined the factors influencing adherence to diet in patients with classical galactosemia. To our knowledge, this review is the first to synthesize determinants of dietary adherence in classical galactosemia using a socio-ecological framework, highlighting multi-level gaps that may inform intervention design and future research. Previously, one study assessed factors affecting low phenylalanine diets in patients with phenylketonuria [24]. Only a limited number of studies met the inclusion criteria, reflecting the scarcity of adherence-focused research in classical galactosemia. Notably, none of the included studies were conducted in low-income countries, highlighting an important geographic gap in the literature and the need for broader global investigation.

This review extends adherence research in inherited metabolic disorders by demonstrating that dietary management in classical galactosemia is not solely an individual responsibility but an ecologically embedded behavior shaped by interacting determinants across family, healthcare systems, and structural

environments. The socio-ecological synthesis highlights that adherence is constrained not only by patient motivation but also by systemic variability in dietary guidance, cultural food environments, and continuity of specialist care.

There are several factors that affect galactosemia patients' dietary adherence, and they can be categorized as psychosocial, cultural, emotional, caregiver and healthcare professional related. Collectively, these factors illustrate the complexity of sustaining strict lifelong dietary management for this rare metabolic disorder. The review found that patients frequently experience social and emotional burdens as a result of dietary restrictions, including feelings of isolation, stigma, and distress in social environments [14]. These findings indicate that dietary restrictions substantially affect patients' emotional and social well-being. Additionally, adherence tended to decline with age [11], reflecting the challenges of independence during adolescence and adulthood. As individuals mature, their social lives become more independent and food-centric, involving peer interactions, dining out, and cultural celebrations. This suggests that psychosocial interventions and peer-support mechanisms may be essential for maintaining



**Fig. 2.** Semi-quantitative socio-ecological mapping of determinants of dietary adherence in classical galactosemia. (Study-specific proportions (n/N, %) of reported psychosocial, interpersonal, healthcare, and structural challenges are displayed. Values are derived from individual studies and are not pooled estimates.).

long-term adherence. Furthermore, patients with galactosemia experience difficulties in relationships, which may stem from following a diet that sets them apart from others, similar to what has been reported in phenylketonuria [25]. Moreover, patients described a sense of being different, often experiencing social isolation and difficulty forming friendships [23]. This inherent pressure to conform to social norms and avoid stigma can directly result in intentional or unintentional deviations from the prescribed diet, as individuals may prioritize social acceptance over strict adherence. Together, these social and emotional pressures may create a reinforcing cycle in which psychological burden undermines motivation and self-efficacy, ultimately compromising adherence. When individuals experience distress, isolation, or general unhappiness due to dietary restrictions, their motivation, self-efficacy, and capacity to consistently adhere to the diet diminish.

This review showed that caregiver knowledge, confidence, and ability to manage the diet significantly influenced adherence [21]. Another systematic review demonstrated a similar finding where knowledge level about the diet was significantly associated with

adherence in patients with phenylketonuria [24]. One study emphasized that the success of dietary treatment for classical galactosemia depends largely on the parents' knowledge of the disease, their ability to discipline the child, and their capacity to follow the diet strictly [26]. Overprotective behaviors and excessive anxiety of caregivers were associated with behavioral challenges and reduced compliance. These findings align with broader evidence from pediatric chronic illness, where caregiver stress and mental health directly affect treatment adherence [27]. Although adherence was not directly assessed, cognitive and functional impairments in adulthood may limit independent dietary management, underscoring the continued importance of caregiver and support systems [28]. As children grow older, the responsibility for adherence gradually shifts from caregivers to the patient, highlighting the importance of preparing families for this transition through education and psychological support.

Another critical finding was the variation in health professionals' roles toward the necessity of strict dietary management [22]. Centers and dietitians differed in their recommendations regarding the inclusion or exclusion of specific foods, with some



promoting a relaxed lactose-free diet with trace amounts of lactose in manufactured food while others permitted a lactose-free diet with all fruits, vegetables and galactosidase. The majority of centers (67 %) reported annual dietary monitoring by dietitians. However, 32 % of patients were lost to follow-up. Such inconsistencies in professional management may negatively influence dietary adherence. A similar finding was reported in another study that variation in dietary recommendations between countries and treatment centers creates confusion for patients or caregivers and may influence adherence [29]. Another study reported that caseinates, certain hard cheeses, and legumes contained low galactose levels comparable to permitted foods in the diet, suggesting that including these items could enhance nutrient intake and improve dietary adherence in galactosemia patients [30]. A study demonstrated that hypo glycosylation in classical galactosemia is influenced by diet and may deteriorate with higher galactose exposure from poor adherence or liberalization, contributing to endocrine complications in females [31]. This underscores the importance of strict dietary management for both metabolic stability and long-term endocrine health. These findings highlight the urgent need for international consensus guidelines that are evidence-based and consistently communicated to patients and families.

These findings suggest that adherence interventions should move beyond education-based models and incorporate caregiver support, psychosocial counseling, structured transition services, and standardized professional guidance. Interventions addressing social participation and emotional burden may be as critical as dietary prescription itself.

Beyond identifying individual determinants, this review contextualizes dietary adherence within a socio-ecological framework, demonstrating that management in classical galactosemia is shaped by interacting influences across multiple levels. Although earlier sections describe caregiver, psychosocial, cultural, and emotional influences, the SEM synthesis shows these factors operate interactively rather than in isolation. Individual psychological burden and quality-of-life impairments intersect with prolonged caregiver dependence, social participation constraints, variability in healthcare practices, and broader structural challenges such as employment and food environments. This multi-level perspective suggests that interventions focusing solely on dietary education or individual responsibility may be insufficient to support long-term dietary management. Instead, coordinated, lifespan-oriented approaches that integrate psychosocial support, consistent clinical follow-up, and contextual sensitivity may be better suited to addressing the complex realities faced by individuals with classic galactosemia and their families.

The included studies revealed meaningful cross-cultural variation in dietary management practices and social context. International surveys demonstrated differences in restriction strictness, monitoring frequency, and professional conviction regarding lifelong dietary exclusion. These variations likely reflect differences in national guidelines, healthcare infrastructure, and cultural dietary patterns. In dairy-centered food cultures, social participation may be particularly challenging, as galactose-containing foods are embedded in common social rituals and shared meals. Furthermore, differences in food labeling standards, access to lactose-free alternatives, and financial reimbursement policies may influence adherence feasibility across countries. For example, adults in the German cohort reported additional monthly dietary costs [14], while caregivers in the United Kingdom reported substantial concern regarding food safety in social environments [21]. These contextual differences suggest that dietary adherence in classical galactosemia cannot be interpreted independently of cultural and healthcare system structures.

In line with international clinical guidelines for classical galactosemia [32], dietary management should be approached as a lifelong, multidisciplinary process that extends beyond simple restriction of lactose-containing dairy products. Effective clinical care requires clear and consistent dietary counseling, regular nutritional monitoring, and structured transition planning from pediatric to adult services. Given the psychosocial and contextual challenges identified in this review, metabolic teams should incorporate individualized education, practical training for navigating social eating environments, and access to psychosocial support. Educational intervention should extend beyond early childhood counseling to include ongoing, age-appropriate education that supports self-management skills. Structured transition programs are particularly important to prepare adolescents for independent dietary management in adulthood. Integrating metabolic specialists, dietitians, and mental health professionals within a coordinated care model may enhance long-term adherence and reduce treatment burden across the lifespan.

However, this study features several limitations that should be addressed. As galactosemia is a rare disease, recruitment is inherently constrained, often leading to small sample sizes. Such limited datasets reduce statistical power and may hinder the detection of significant differences or associations.

Our findings are limited by the heterogeneity of the included studies, including differences in study design, populations, and adherence assessment methods. All studies were cross-sectional and primarily relied on self-reported data, increasing susceptibility to recall bias, social desirability bias, and selection bias while limiting control for confounding factors. The absence of standardized adherence measures further restricts comparability across studies, and the lack of longitudinal data limits understanding of long-term adherence patterns and outcomes.

Most studies relied on self-reported questionnaires completed by patients or caregivers, with no standardized or validated adherence instrument specific to classical galactosemia identified. One study utilized the Quality-of-Life Profile for the Chronically Ill (PLC), which assesses psychosocial functioning rather than dietary compliance. In another study, adherence was reported by healthcare professionals based on clinical follow-up rather than patient-level dietary monitoring. None of the included studies employed objective biochemical markers, structured dietary logs, or validated adherence scales. This heterogeneity limits comparability across studies and raises concerns regarding recall bias, social desirability bias, and potential overestimation of adherence. The absence of standardized adherence measurement tools represents a significant methodological gap in the literature and complicates efforts to identify robust determinants of long-term dietary management in classical galactosemia.

Future research should prioritize theory-informed, longitudinal investigations that directly assess dietary adherence behavior in individuals with classical galactosemia. Current evidence is largely derived from psychosocial and quality-of-life studies, highlighting a substantial gap in adherence-specific research. The socio-ecological synthesis presented here indicates that adherence is shaped by interacting influences at individual, interpersonal, healthcare, and structural levels. Accordingly, future studies should incorporate validated adherence measures, caregiver and family dynamics, access to specialized metabolic services, and social participation challenges into analytic models. Intervention research should move beyond patient education alone and evaluate multi-level strategies that integrate psychosocial support, structured transition services, standardized dietary counseling, and policies that improve access to suitable foods. Such approaches may help clarify causal pathways and support the

development of comprehensive, sustainable adherence interventions in rare metabolic disorders.

Finally, Greater international consensus on dietary management is needed to reduce inter-center variability that may confuse patients and hinder adherence. A coordinated multinational response is necessary to improve dietary adherence and long-term health outcomes in patients with classical galactosemia. Such a response requires robust, evidence-based approaches to standardize dietary management, monitor adherence, and reduce unnecessary variability across treatment centers. Ultimately, aligning research, clinical practice, and policy at both global and national levels is critical to ensuring equitable care and improved quality of life for individuals with galactosemia.

## 5. Conclusion

This review reframes dietary adherence in classical galactosemia as a multi-level behavioral outcome rather than a purely nutritional task. Although direct evidence on adherence determinants remains limited, the synthesis of psychosocial, familial, healthcare, and contextual factors suggests that long-term dietary management is influenced by a complex ecological system surrounding the patient. Psychological burden, social participation constraints, caregiver involvement, and variability in healthcare support emerged as key contextual influences that may affect the capacity to sustain dietary restriction. By applying a socio-ecological framework, this review provides a structured understanding of how diverse determinants intersect, while also exposing critical evidence gaps. Addressing adherence in classical galactosemia therefore requires integrated strategies that extend beyond individual-level education to encompass family support, psychosocial care, and system-level improvements in metabolic healthcare delivery.

## Author contributions

The authors' responsibilities were as follows - MMH and UD designed the research; AR developed the search strategy; MMH and MABH conducted the literature search; NSN, AD, FA, NNR, PC, MA, TS removed the duplicate studies, conducted the abstract and full text review of the selected articles; UD, AR acted as the third reviewers to assist with any disagreements; AR and MMH completed the analysis of the selected studies; UD, AR, NSN, AD, FA, NNR, PC, and MA wrote the manuscript; MMH and MABH assisted in editing and finalizing the manuscript; AR had primary responsibility for final content. All authors read and approved the final manuscript.

## Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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## Declaration of interest

No potential conflict of interest was reported by the authors.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2026.103109>.

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