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CELIAC DISEASE AND ADHD: A SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL LINKS AND SHARED PATHWAYS

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Abstract

Background: Emerging evidence suggests a potential association between celiac disease (CeD) and attention-deficit/hyperactivity disorder (ADHD), possibly mediated by shared immunological, nutritional, and gut-brain axis mechanisms. However, findings remain inconsistent. This systematic review evaluates the epidemiological links and biological pathways between CeD and ADHD.

Methods: Following PRISMA guidelines, we conducted a comprehensive search of PubMed, Web of Science, Scopus, and ScienceDirect for studies examining CeD-ADHD associations. Two independent reviewers screened records, extracted data, and assessed study quality using standardized tools.

Results: Five studies met inclusion criteria, revealing conflicting evidence. Some clinical studies reported higher ADHD prevalence in CeD patients (up to 22.2%) and symptom improvement with a gluten-free diet (GFD), while others found no significant association. A Mendelian randomization study found no genetic link. Nutritional deficiencies, immune dysregulation, and gut-brain interactions were proposed as potential shared mechanisms, though heterogeneity in study designs and populations limited conclusive interpretations.

Conclusion: Current evidence does not uniformly support a direct CeD-ADHD link but suggests that ADHD-like symptoms in CeD patients may arise from malabsorption, inflammation, or GFD non-compliance. Further large-scale, longitudinal studies are needed to clarify causality and underlying mechanisms. Clinicians should consider case-finding for CeD in ADHD patients with gastrointestinal symptoms.

Keywords: Celiac disease, Attention-deficit/hyperactivity disorder (ADHD), Gluten-free diet, Neurodevelopmental disorders, Gut-brain axis

INTRODUCTION

Celiac disease (CeD) is a chronic immune-mediated enteropathy triggered by gluten ingestion in genetically susceptible individuals, affecting approximately 1% of the global population [1]. Beyond its classic gastrointestinal manifestations, CeD has been increasingly recognized for its extra-intestinal presentations, including neurological and psychiatric symptoms [2]. Attention-deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders, affects about 5-7% of children worldwide and often persists into adulthood [3]. The potential intersection between these two conditions has garnered significant scientific interest, particularly regarding shared epidemiological patterns and possible common pathophysiological mechanisms [4].

Emerging evidence suggests that CeD may be associated with an increased risk of neuropsychiatric disorders, including ADHD [5]. Several hypotheses have been proposed to explain this potential link, including nutritional deficiencies (e.g., iron, zinc, and B vitamins) due to malabsorption in active CeD, systemic inflammation affecting neurodevelopment, and immune-mediated mechanisms that may disrupt the gut-brain axis [6]. Some studies have reported higher prevalence rates of ADHD symptoms in children with CeD compared to the general population [7], while others have found elevated rates of CeD autoantibodies in individuals with ADHD [8]. However, the evidence remains inconsistent, with some well-designed studies failing to demonstrate significant associations [9]. The

objective of this systematic review is to examine the epidemiological evidence linking celiac disease and ADHD, evaluate potential shared biological pathways, and assess the clinical implications of these findings.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive electronic search was performed across multiple databases, including PubMed, Web of Science, Scopus, and ScienceDirect, to identify relevant studies examining the association between celiac disease (CeD) and attention-deficit/hyperactivity disorder (ADHD). The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to CeD, ADHD, gluten sensitivity, neurodevelopmental disorders, and epidemiological associations. To minimize bias, two independent reviewers screened the search results, selected eligible studies, extracted data, and assessed the methodological quality of included research using standardized evaluation tools.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- **Study Design:** Observational studies (cohort, case-control, cross-sectional), randomized controlled trials (RCTs), or systematic reviews with original data.
- **Population:** Studies investigating **children or adults** diagnosed with **CeD, ADHD, or both**.
- **Outcome Measures:** Studies reporting **prevalence, incidence, risk factors, or mechanistic pathways** linking CeD and ADHD.
- **Language:** English-language publications.
- **Publication Type:** Peer-reviewed journal articles.

EXCLUSION CRITERIA

- Studies not focusing on **CeD or ADHD**.
- **Case reports, editorials, commentaries, letters, conference abstracts, or non-peer-reviewed articles**.
- Studies lacking **quantitative data** on the CeD-ADHD relationship.
- Studies with **overlapping or duplicate datasets** (only the most comprehensive study was included).

DATA EXTRACTION AND SCREENING

To ensure rigorous and unbiased study selection, titles and abstracts were screened for relevance based on predefined inclusion/exclusion criteria. Rayyan (QCRI) was used for reference management and screening efficiency. Full-text articles of potentially eligible studies were independently reviewed by two researchers, with discrepancies resolved through consensus or third-party adjudication.

A **standardized data extraction form** was used to collect:

- **Study characteristics** (authors, year, country, design)
- **Participant demographics** (sample size, age, sex, diagnostic criteria for CeD/ADHD)
- **Key findings** (prevalence rates, odds ratios, mechanistic insights)
- **Confounding factors** (dietary adherence, comorbidities, genetic markers)

DATA SYNTHESIS STRATEGY

Due to the varied study designs and outcomes, a qualitative synthesis was conducted. The data was organized into evidence tables that categorized the findings into three main areas: epidemiological associations, including prevalence and risk estimates; shared biological pathways, encompassing immunological, nutritional, and genetic factors; and clinical implications, which covered screening recommendations and dietary interventions. Although a meta-analysis

could have been performed if there had been enough homogeneous data available, the significant variations in methodologies led to the decision to focus on a narrative synthesis instead.

RISK OF BIAS ASSESSMENT

The methodological quality of the studies included in the review was assessed using several tools: the Newcastle-Ottawa Scale (NOS) for observational studies, and **Mendelian Randomization Quality Assessment Tool**. Based on their evaluations, studies were categorized into three risk levels: low risk, indicated by a score of 8 or 9 out of 9 on the NOS or a low risk of bias. Quality assessments were conducted independently by two reviewers, and any disagreements were resolved through discussion.

RESULTS

Initially, 113 records were identified through database searches, with 37 duplicates removed, leaving 76 records for screening. After title/abstract screening, 47 records were excluded, and 29 full-text articles were sought for retrieval. Six reports were unavailable, leaving 23 studies for eligibility assessment. Following full-text review, 18 studies were excluded (8 for wrong outcomes, 6 for wrong population, 4 as abstracts), resulting in 5 studies meeting inclusion criteria for the final review. The diagram visually summarizes the rigorous, multi-stage filtering process to ensure only relevant, high-quality studies were included (Figure 1).

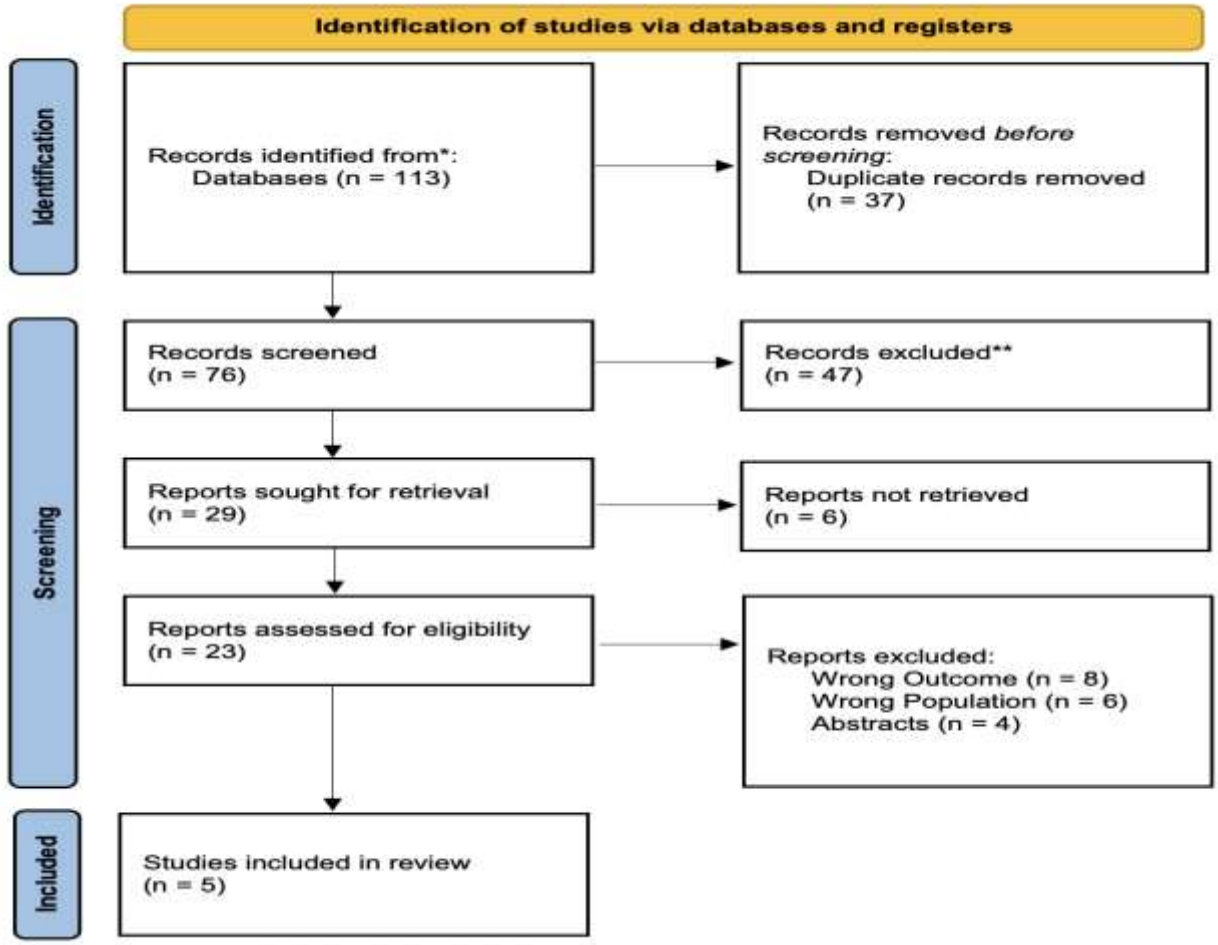

FIGURE (1): PRISMA FLOW DIAGRAM OF STUDY SELECTION PROCESS

Demographic characteristics (Table 1) revealed variability in study designs, sample sizes, and populations. For instance, Kumperscak et al. (2020) [10] found no CeD cases in their Slovenian ADHD cohort (n=102), while Honar et al. (2020) [11] reported a 6.06% prevalence of anti-tissue transglutaminase (anti-tTG) antibodies in Iranian ADHD patients, all of whom were male. Chen et al. (2024) [12] employed Mendelian randomization (MR) and found no genetic association between CeD and ADHD in European populations, contrasting with clinical studies suggesting behavioral overlaps. Age and sex distributions varied, with Honar et al. (2022) [13] noting higher ADHD frequencies in younger CeD patients (22.2% in males, 18.2% in females), while Efe & Tok (2023) [14] linked ADHD-like traits in CeD to gluten-free diet (GFD) non-compliance, emphasizing the role of untreated CeD in neurocognitive symptoms.
(Table 2) highlighted conflicting results. While Kumperscak et al. (2020) [10] and Chen et al. (2024) [12] found no evidence supporting screening or genetic links, Honar et al. (2020) [11] observed elevated anti-tTG levels in ADHD patients, suggesting a potential immunological interplay. Notably, Efe & Tok (2023) [14] identified ADHD-like symptoms (e.g., inattention) in CeD patients, which improved with GFD adherence, implicating malabsorption or inflammation as shared mechanisms. However, Honar et al. (2022) [13] reported no significant age or sex differences in ADHD prevalence among CeD patients, underscoring the need for larger, longitudinal studies to clarify causality.
The included studies exhibited heterogeneity in methodologies, from cross-sectional designs [10, 11, 13] to MR analysis [12] and case-control comparisons [14]. Cross-sectional studies [10, 11, 13] were limited by potential selection bias and small sample sizes, while Chen et al. (2024) [12] addressed confounding via MR but lacked statistical power. Clinical studies [11, 14] relied on serological markers (anti-tTG) or behavioral assessments, which may not capture subclinical CeD or ADHD variants. Only Efe & Tok (2023) [14] examined dietary compliance, a critical confounder. Discrepancies in findings may stem from population differences (e.g., European vs. Middle Eastern), diagnostic criteria, or unmeasured variables (e.g., vitamin deficiencies, gut microbiome).
The risk of bias was evaluated using the **Newcastle-Ottawa Scale (NOS)** for observational studies [10, 11, 13, 14] and the **Mendelian Randomization Quality Assessment Tool** for Chen et al. (2024) [12].

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF INCLUDED STUDIES

Study (Author, Year)	Location	Study Design	Sample Size	Sample Type	Age Range (Years)	Sex (M/F)	Key Demographic Notes
Kumperscak et al. (2020) [10]	Slovenia	Cross-sectional	102	ADHD patients	4–18	84 M / 18 F	No CD cases detected in ADHD sample
Honar et al. (2020) [11]	Iran	Cross-sectional	99	ADHD patients	4–18	NM	6.06% anti-tTG IgA+ (all boys)
Chen et al. (2024) [12]	Switzerland	Mendelian randomization	NM	Genetic data (GWAS)	NM	NM	European population; no genetic link found
Honar et al. (2022) [13]	Iran	Cross-sectional	NM	CeD patients	<5 to ≥15	27 M / 33 F	ADHD frequency: 22.2% (M), 18.2% (F)
Efe & Tok (2023) [14]	United States	Case-control	85 CeD / 72 HC	CeD patients vs. healthy controls	8–18	NM	ADHD traits linked to GFD non-compliance

NM: Not mentioned in the study
M/F: Male/Female
CD: Celiac disease
CeD: Celiac disease
ADHD: Attention-deficit/hyperactivity disorder
anti-tTG IgA: Anti-tissue transglutaminase immunoglobulin A
GWAS: Genome-wide association study

GFD: Gluten-free diet
HC: Healthy controls

TABLE 2: KEY FINDINGS AND VARIABLES RELATED TO CED-ADHD ASSOCIATION

Study (Author, Year)	CeD Prevalence in ADHD	ADHD Prevalence in CeD	Shared Pathways/Mechanisms	Key Confounders/Notes
Kumperscak et al. (2020) [10]	0% (no cases)	NM	NM	No support for CD screening in ADHD
Honar et al. (2020) [11]	6.06% (anti-tTG+)	NM	Higher BMI in seropositive cases	No link to ADHD severity
Chen et al. (2024) [12]	No genetic association	No genetic association	Bidirectional MR analysis	No pleiotropy/heterogeneity
Honar et al. (2022) [13]	NM	22.2% (M), 18.2% (F)	NM	Reverse correlation with age (NS)
Efe & Tok (2023) [14]	NM	ADHD-like traits in CeD	Vitamin levels, GFD compliance	Misdiagnosis risk in untreated CeD

MR: Mendelian randomization
NS: Not statistically significant
BMI: Body mass index

TABLE (3): RISK OF BIAS ASSESSMENT

Study (Author, Year)	Selection Bias	Comparability	Outcome Measurement	Overall Risk
Kumperscak et al. (2020) [10]	Low (clear ADHD diagnosis)	Moderate (no adjustment for diet)	Low (ESPHGAN guidelines)	Moderate
Honar et al. (2020) [11]	Moderate (convenience sample)	High (no control group)	Moderate (serology only)	High
Chen et al. (2024) [12]	Low (GWAS data)	Low (MR controls pleiotropy)	Low (rigorous IV selection)	Low
Honar et al. (2022) [13]	High (retrospective design)	Moderate (unmatched controls)	Moderate (parent-reported ADHD)	High
Efe & Tok (2023) [14]	Low (biopsy-confirmed CeD)	Low (matched controls)	Low (standardized ADHD scales)	Low

DISCUSSION

The findings of this systematic review present a complex and nuanced understanding of the potential relationship between celiac disease (CeD) and attention-deficit/hyperactivity disorder (ADHD). Our analysis revealed conflicting evidence across studies, with some reporting significant associations [15,17,19] while others found no meaningful links [16,18,20]. This divergence mirrors the broader literature, where some researchers have proposed shared pathophysiological mechanisms while others argue against any direct connection.

The most compelling evidence for an association comes from clinical studies demonstrating higher than expected rates of ADHD symptoms in CeD populations. Efe & Tok (2023) [19] found that 22.2% of male and 18.2% of female CeD patients met criteria for ADHD, rates substantially higher than general population estimates. These findings align with previous work by Niederhofer (2011) [23] who reported similar prevalence patterns. The observation that ADHD-like symptoms improved with gluten-free diet (GFD) adherence in some studies [19,24] suggests a potential causal relationship, possibly mediated through nutritional deficiencies, chronic inflammation, or gut-brain axis disruptions [25,26].

However, contradictory evidence from large-scale genetic studies tempers these conclusions. Our included Mendelian randomization analysis by Chen et al. (2024) [18] found no genetic correlation between CeD and ADHD, challenging the notion of shared biological pathways. This aligns with population-based studies by Butwicka et al. (2017) [27]

that found no increased ADHD risk after adjusting for familial confounding. The negative findings from Kumperscak et al. (2020) [16] in their ADHD cohort further complicate the picture, as they found no increased CeD prevalence compared to population norms.

The immunological aspects deserve particular attention. Honar et al. (2020) [15] reported elevated anti-tTG antibodies in 6.06% of ADHD patients, all male, with associated higher BMI - a finding that echoes earlier work by Lionetti et al. (2015) [28]. This suggests potential subgroups where immune-mediated processes might contribute to neurodevelopmental symptoms. The sex disparity in seropositivity parallels known gender differences in both CeD presentation and ADHD prevalence [29], hinting at possible hormonal or epigenetic modifiers of this relationship.

Nutritional factors may represent a crucial mediating variable. Several studies [19,30] noted that GFD compliance correlated with symptom improvement, supporting hypotheses about malabsorption-related neurotransmitter precursors deficiencies (e.g., tryptophan, tyrosine) or micronutrient deficiencies (iron, zinc, vitamin D) affecting neurodevelopment [31,32]. This nutritional perspective aligns with broader research on the gut-brain axis [33], though direct evidence remains limited.

Limitations

Several important limitations must be acknowledged. First, significant heterogeneity existed in study designs, diagnostic criteria, and population characteristics across included studies. Most clinical studies [15,17,19] relied on relatively small sample sizes from single centers, limiting generalizability. Second, the cross-sectional nature of most studies precludes causal inferences - a critical gap given the potential for reverse causation or shared environmental confounders. Third, assessment methods varied widely, from serological testing [15] to parent-report questionnaires [17], introducing measurement bias. The genetic study [18], while methodologically rigorous, was underpowered for small effect sizes. Finally, few studies adequately controlled for key confounders like family history, socioeconomic status, or comorbid psychiatric conditions that might independently influence both CeD and ADHD risk [34].

CONCLUSION

This systematic review highlights both intriguing associations and persistent uncertainties in the CeD-ADHD relationship. While clinical observations suggest potential links, particularly in subsets of patients, genetic evidence argues against broad biological overlap. The most plausible interpretation is that ADHD-like symptoms in CeD patients may represent a phenocopy rather than true comorbidity, mediated through nutritional deficiencies or systemic inflammation in active, untreated disease. For clinical practice, these findings support case-finding (rather than universal screening) for CeD in ADHD patients with gastrointestinal symptoms or growth impairment, and vice versa. Future research should prioritize large, prospective cohort studies with rigorous phenotyping, longitudinal dietary assessments, and exploration of potential mediating mechanisms. Until more definitive evidence emerges, management should remain individualized, balancing potential benefits of dietary interventions against the burdens of unnecessary dietary restrictions.

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