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Review Article

An updated meta-analysis on the association between celiac disease and cardiovascular diseases

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Abstract: Objectives: Research on the relationship between celiac disease (CD) and cardiovascular disease (CVD) is still ongoing, and different studies have reported contradictory findings. To carry out a meta-analysis and systematic review to look into the connection between CD and CVD risk. Methods: A thorough search was conducted in PubMed, Scopus, and Google Scholar databases up to February 19, 2024. Relevant articles were extracted, and the titles, abstracts, and full texts of the related articles were screened. The quality of the studies was assessed using the Joanna Briggs Institute critical appraisal tools. Results: Nine cohort and one case-control studies involving 49,621,333 individuals were included in the meta-analysis. The pooled analysis revealed a 7% increased risk of CVD in CD patients compared to controls (OR: 1.07, 95% CI: 1.03-1.10, $P < 0.05$). Significant heterogeneity was observed among studies ($I^2 = 76\%$, $P < 0.001$). Conclusion: This meta-analysis provides evidence of a modest but significant increase in CVD risk in patients with CD. The results highlight the importance of considering cardiovascular health in CD treatment and the need for further research to elucidate the mechanisms underlying this association and to develop targeted prevention strategies.

Keywords: Celiac disease (CD), cardiovascular disease (CVD), coronary artery disease (CAD), systematic review, meta-analysis

Introduction

Celiac disease (CD) is a highly prevalent chronic intestinal disease caused by dietary gluten in genetically susceptible individuals [1]. The prevalence of CD is approximately 1% of the general population in Western countries, and its incidence is rapidly increasing [2]. The pathogenesis of CD is related to immune-mediated mechanisms and over all other systems, the gastrointestinal tract is the most commonly affected by CD. Diarrhea, anemia, weight loss, chronic fatigue, and other intestinal and extraintestinal systemic symptoms are among the primary symptoms of CD [3]. This immune-mediated association is primarily mediated through

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immunse and inflammatory mechanisms elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins have been observed in CD patients. These cytokines lead to endothelial dysfunction, a precursor to atherosclerosis and other cardiovascular morbidities [4]. In addition, chronic inflammation can impair endothelial function, leading to increased vascular permeability, reduced vasodilation, and a pro-thrombotic state. Recent studies have demonstrated that gluten exposure in CD patients induces vascular inflammation and oxidative stress, further exacerbating endothelial dysfunction [5]. Molecular Mimicry and Autoimmune Cardiac Injury can be another mechanism that causes cardiovascular disease (CVD) morbidities [6]. In some cases, a genetic relationship between immune-related genes such as HLA-DQ2 and HLA-DQ8 has been proven [7]. Epidemiological research shows that CD is more commonly found in women and is typically diagnosed in childhood, adolescence, or at ages 40-60 years, but it can also occur throughout the lifetime [8, 9]. Associations between CD and CVD were determined after adjustment for common cardiovascular risk factors [10]. An increased risk of CVD, including ischemic heart disease (IHD) and stroke [9], and consequently higher cardiovascular morbidity and mortality rates, have been observed [11]. Studies have shown that certain cardiovascular morbidities, including cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis, are more prevalent in individuals with CD compared to those without the disease [12]. Recent studies have tended not to explore the role of traditional CVD factors, such as blood pressure or serum total cholesterol, in proving the link between CD and CVD, despite research showing a healthier cardiovascular profile in people with CD [13]. The evidence for an association between CVD and CD is mixed, with positive associations seen in some studies but not in all [14]. It is noteworthy to mention a hypothesis raised by West et al. [15], which found a 40% reduction in IHD mortality in people with diagnosed CD who were fed gluten-free diets.

In this study, we aim to establish the latest evidence of a close association between CD and the increased risk of CVD. We hypothesize that individuals with CD have a higher risk of CVD.

Methods

Study design

This systematic review and meta-analysis aim to explore the association between CD and CVD. Our methodology adheres to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16]. The research protocol for this review was registered on PROSPERO (Registration ID: CRD42024580796).

Search strategy

An advanced literature search was conducted up to February 14, 2024, to retrieve relevant articles from the following databases: PubMed, Scopus, and Google Scholar (**Table 1**). The search strategy comprised two main subgroups of keywords and Medical Subject Headings (MeSH).

The following search terms were used in the Title/Abstract fields from pubmed database: (celiac[Title/Abstract]) OR (coeliac[Title/Abstract]) AND (cardiovascular[Title/Abstract] OR myocardial infarction[Title/Abstract] OR heart failure[Title/Abstract] OR heart[Title/Abstract] OR cardiac[Title/Abstract] OR cardio[Title/Abstract] OR hypertension[Title/Abstract] OR coronary artery disease[Title/Abstract] OR arrhythmia[Title/Abstract] OR heart attack[Title/Abstract] OR heart valve disease[Title/Abstract] OR congenital heart disease[Title/Abstract] OR peripheral artery disease[Title/Abstract] OR aortic disease[Title/Abstract] OR pericardial disease[Title/Abstract] OR deep vein thrombosis[Title/Abstract] OR vasculitis[Title/Abstract] OR cardiac tamponade[Title/Abstract] OR carcinoid heart disease[Title/Abstract] OR cardiomegaly[Title/Abstract] OR cardiomyopathies[Title/Abstract] OR endocarditis[Title/Abstract] OR heart aneurysm[Title/Abstract] OR cardiac arrest[Title/Abstract] OR angioedema[Title/Abstract] OR rheumatic heart disease[Title/Abstract]). Also, search strategies from Scopus and Google Scholar databases are explained in detail in the appendices (**Table 1**).

One subgroup consisted of terms related to CD, while the other included terms related to all types of CVD, such as ischemic heart disease and congenital heart disease. The subgroups

Table 1. Search strategy for selected databases

Search engine	Search strategy	Additional filters	Total results
Pubmed	((celiac[Title/Abstract]) OR (celiac[Title/Abstract])) AND ((cardiovascular[Title/Abstract]) OR ("myocardial infraction"[Title/Abstract]) OR ("heart failure"[Title/Abstract]) OR (heart[Title/Abstract]) OR (cardiac[Title/Abstract]) OR (cardio[Title/Abstract]) OR (hypertension[Title/Abstract]) OR ("coronary artery disease"[Title/Abstract]) OR (arrhythmia[Title/Abstract]) OR ("heart attack"[Title/Abstract]) OR ("heart valve disease"[Title/Abstract]) OR ("congenital heart disease"[Title/Abstract]) OR ("peripheral artery disease"[Title/Abstract]) OR ("aortic disease"[Title/Abstract]) OR ("pericardial disease"[Title/Abstract]) OR ("deep vein thrombosis"[Title/Abstract]) OR (vasculitis[Title/Abstract]) OR ("cardiac tamponade"[Title/Abstract]) OR ("carcinoid heart disease"[Title/Abstract]) OR (cardiomegaly[Title/Abstract]) OR (cardiomyopathies[Title/Abstract]) OR (endocarditis[Title/Abstract]) OR ("heart aneurysm"[Title/Abstract]) OR ("cardiac arrest"[Title/Abstract]) OR (angioedema[Title/Abstract]) OR ("rheumatic heart disease"[Title/Abstract]))	February 14, 2024	1705
Scopus	(TITLE-ABS-KEY (celiac) OR TITLE-ABS-KEY (celiac)) AND (TITLE-ABS-KEY (cardiovascular) OR TITLE-ABS-KEY ("myocardial infraction") OR TITLE-ABS-KEY ("heart failure") OR TITLE-ABS-KEY (heart) OR TITLE-ABS-KEY (cardiac) OR TITLE-ABS-KEY (cardio) OR TITLE-ABS-KEY (hypertension) OR TITLE-ABS-KEY ("coronary artery disease") OR TITLE-ABS-KEY (arrhythmia) OR TITLE-ABS-KEY ("heart attack") OR TITLE-ABS-KEY ("heart valve disease") OR TITLE-ABS-KEY ("congenital heart disease") OR TITLE-ABS-KEY ("peripheral artery disease") OR TITLE-ABS-KEY ("aortic disease") OR TITLE-ABS-KEY ("pericardial disease") OR TITLE-ABS-KEY ("deep vein thrombosis") OR TITLE-ABS-KEY (vasculitis) OR TITLE-ABS-KEY ("cardiac tamponade") OR TITLE-ABS-KEY ("carcinoid heart disease") OR TITLE-ABS-KEY (cardiomegaly) OR TITLE-ABS-KEY (cardiomyopathies) OR TITLE-ABS-KEY (endocarditis) OR TITLE-ABS-KEY ("heart aneurysm") OR TITLE-ABS-KEY ("heart arrest") OR TITLE-ABS-KEY (angioedema) OR TITLE-ABS-KEY ("rheumatic heart disease") OR TITLE-ABS-KEY (angina))	February 15, 2024	6120
Google Scholar	allintitle: celiac cardiovascular OR "myocardial infraction" OR heart OR cardio OR cardiac OR "heart failure" OR hypertension OR "coronary artery disease" OR arrhythmia OR "heart attack" OR "heart valve disease" OR "congenital heart disease" OR "peripheral artery disease" OR "aortic disease" OR "pericardial disease" OR "deep vein thrombosis" OR vasculitis OR "cardiac tamponade" OR "carcinoid heart disease" OR cardiomegaly OR cardiomyopathies OR endocarditis OR "heart aneurysm" OR "heart arrest" OR angioedema OR "rheumatic heart disease" OR angina	February 14, 2024	212
	allintitle: celiac cardiovascular OR "myocardial infraction" OR heart OR cardio OR cardiac OR "heart failure" OR hypertension OR "coronary artery disease" OR arrhythmia OR "heart attack" OR "heart valve disease" OR "congenital heart disease" OR "peripheral artery disease" OR "aortic disease" OR "pericardial disease" OR "deep vein thrombosis" OR vasculitis OR "cardiac tamponade" OR "carcinoid heart disease" OR cardiomegaly OR cardiomyopathies OR endocarditis OR "heart aneurysm" OR "heart arrest" OR angioedema OR "rheumatic heart disease" OR angina	February 14, 2024	51

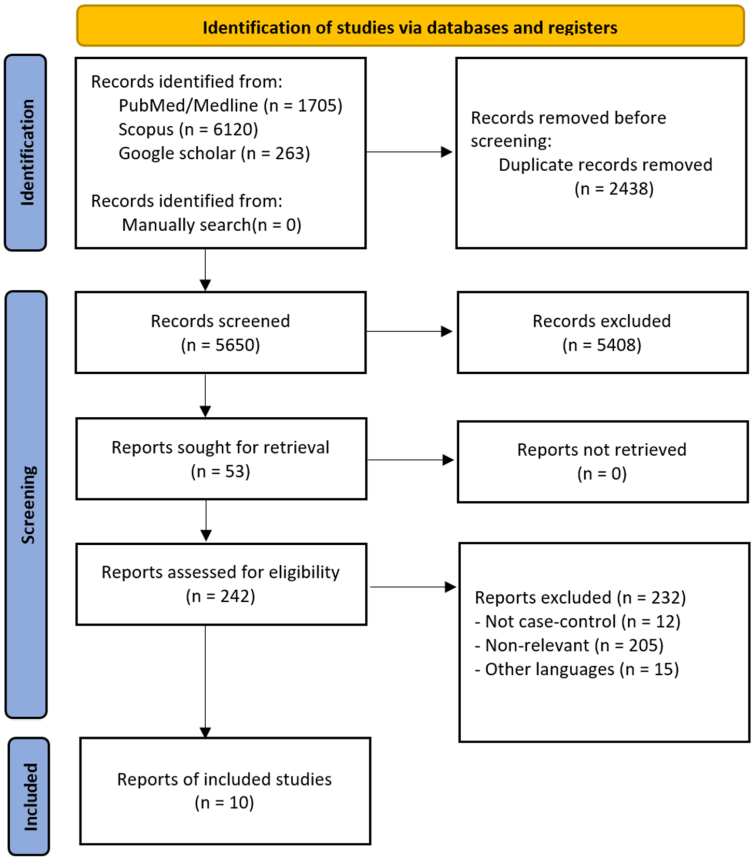

Figure 1. PRISMA flow diagram.

were combined using the 'AND' operator, and no restrictions were applied regarding the date, publication type, or language. The search strategy was modified according to the query format of each database. To lower the risk of missing relevant papers, we screened the reference lists of relevant systematic reviews and included studies that were assessable in our study. All steps were independently conducted by two reviewers, and any disputes were resolved through discussion between the reviewers.

Inclusion and exclusion criteria inclusion criteria

For studies to be included in this meta-analysis, the following criteria had to be met: 1. Observational methodology (to exclude the confounding effect of any intervention). 2. The main focus of the study was to investigate the link between CD and CVD. 3. The study population consisted of patients diagnosed with CD.

Studies that used other types of methodology or were performed on animal models were excluded.

Data extraction and synthesis

Two independent reviewers assessed each study's title and abstract to determine its eligibility for inclusion in this meta-analysis. Studies that did not fulfill our criteria were excluded. The full text of the remaining studies was screened, and eligible studies entered the data extraction process. The following items were obtained for extraction in four sets: 1. Study characteristics (i.e., authors, location, year, and type of study). 2. Patient-specific factors (i.e., the eligibility criteria for included cases). 3. Study design (i.e., number of participants, method and period of sampling, diagnosis of CD). 4. Outcomes (i.e., rate of CVD).

Quality assessment and bias evaluation

The two aforementioned reviewers used the critical appraisal checklists for cohort and case-control, developed by the Joanna Briggs Institute (JBI) (https://jbi.global/critical-appraisal-tools). A third author was involved in the process in case of disparity.

Statistical analysis

We used STATA 13.1 software, developed by StataCorp LP in College Station, TX, USA, for our data analysis. Results were reported as pooled odds ratios (ORs) with a 95% confidence interval (CI), visualized in a forest plot. We evaluated heterogeneity among the eligible studies using the I^2 statistic [17] and used the random effects model when significant heterogeneity was detected ($I^2 > 50\%$) [18]. Finally, we performed a sensitivity analysis, excluding one study at a time and repeating the meta-analysis. This allowed us to ensure the reliability of our findings.

The statistical significance level was established at $P < 0.05$.

Results

Study selection and characteristics

A PRISMA flow diagram (**Figure 1**) illustrates the exclusion and screening process. Initial searches on PubMed, Scopus, and Google Scholar identified 8,088 potentially relevant papers, of which 2,438 were duplicates and subsequently excluded. After reviewing the abstracts and titles of the remaining 5,650 papers, we excluded 5,408 as unrelated to the review. We then obtained and evaluated 242 full-text papers, excluding 232 primarily for not having relevant outcomes. Ultimately, 10 studies were deemed eligible and included in the review and meta-analysis.

Baseline characteristics

This systematic review encompassed 10 articles, involving a total population of 49,621,333 individuals diagnosed with CD. The mean age for the CD group is 42.76 years (95% CI: 16.62-68.90), and for the CVD group, it is 56.36 years (95% CI: 48.33-64.39). The studies spanned from 2007 to 2023, providing a comprehensive time range for analysis. Studies were conducted in multiple countries, including five studies Sweden [14, 19-22], two studies from the United Kingdom [9, 23], one from Italy [24], one from the United States of America [11], and one from Denmark [25]. All studies were either cohort or case-control studies. The primary objective was to evaluate the risk of CVD in this specific population. The detailed characteristics are comprehensively presented in **Table 2**.

Quality assessment

All ten studies evaluated in our analysis were subjected to quality assessment utilizing the JBI Critical Appraisal Tools. Of these, nine were conducted as cohort studies, while one was conducted as a case-control study. Overall, the methodological quality of the studies was deemed to be satisfactory.

All nine cohort studies satisfied the requirements pertaining to group homogeneity and recruiting from the same population. The measurement of exposure was consistently applied in both exposed and unexposed groups across all studies. Eight out of nine studies acknowledged and appropriately controlled for confounding variables. Furthermore, all studies had adequate follow-up periods and utilized valid outcome measurements. The statistical analyses conducted were deemed to be suitable in all instances.

The single case-control study included in the review met all quality criteria concerning appropriate matching of cases and controls, consistent measurement of exposure, and evaluation of confounding between exposure and outcomes.

A detailed quality assessment of the studies included can be located in **Table 3**.

Primary outcome

Association between CD and CVD Meta-analysis of the included studies revealed a statistically significant association between CD and an increased risk of CVD. According to **Figure 2**, the pooled OR was 1.07 (95% CI: 1.03-1.10, $P < 0.05$), indicating a 7% higher risk of CVD in individuals with CD compared to controls.

Heterogeneity assessment

Significant heterogeneity was observed among the studies ($I^2 = 76\%$, $P < 0.001$). The Galbraith plot analysis (**Figure 3**) identified three studies as potential outliers contributing to this heterogeneity. Sensitivity analysis excluding these studies did not substantially alter the main effect estimate (adjusted OR: 1.05, 95% CI: 1.02-1.08).

Publication bias

Assessment of publication bias using Egger's test yielded a coefficient of -0.073 (95% CI: -0.183-0.037, $P = 0.194$), suggesting no significant small-study effects. The funnel plot analysis (**Figure 4**) corroborated this finding, displaying reasonable symmetry around the pooled effect estimate.

Discussion

Summary of findings

This comprehensive meta-analysis, including 10 cohort and case-control studies in a total

Table 2. Baseline characteristics of the included studies

Author/ reference	Year	Country	Study design	Participants	Mean/median age	Sex (female)	Was there an association between celiac disease and cardiovascular diseases?	Cardiovascular disease
Dore et al. [28]	2023	Italy	Retrospective case-control study	Case: Patients with CVD (n = 2503) Control: Patients without CVD (n = 5992)	Case: 65.4 ± 11.8 years Control: 46.5 ± 16.1 years	Case: 1537 (61.4%) Control: 3957 (66.0%)	Yes, CD significantly reduced the risk of CVD (OR 0.30, 95% CI 0.22-0.41).	Atherosclerosis, arrhythmias, valvular heart disease, cardiomyopathies, hypertension
Conroy et al. [9]	2022	UK	Prospective analysis of a large cohort study	Case: 2,083 with CD Control: 467,012 without CD	Case: 58.1 years Control: 56.7 years	Case: 1,489 (71.5%) Control: 260,471 (55.8%)	Yes, CD was associated with an increased risk of CVD.	CVD, IHD, MI, stroke
Karhus et al. [25]	2020	Denmark	Population-based cohort study	Case: 169 with undiagnosed CD Control: 16,607 without CD	Case: 49.0 years Control: 48.0 years	Case: 85 (50.3%) Control: 9,434 (56.8%)	Yes, undiagnosed CD was associated with an increased risk of CVD.	Not specified
Gajulapalli and Pattanshetty [11]	2017	USA	Cross-sectional retrospective cohort study	Case: 59,010 patients with CD Control: 48,583,280 patients without CD	Case: 50.6 years Control: 53.1 years	Case: 56.7% women (2,914/5,140) Control: 40.2% women (851,862/2,119,060)	Yes, there was a significant association.	Coronary artery disease
Emilsson et al. [14]	2015	Sweden	Nationwide cohort study	Case: 430 celiac patients with MI Control: 1988 general population controls with MI	Not specified	Case: 31.0% (13 out of 42) at 6-10 weeks follow-up, 33.3% (11 out of 33) at one-year follow-up Control: 37.8% (76 out of 201) at 6-10 weeks follow-up, 35.8% (54 out of 151) at one-year follow-up	Yes, celiac patients with MI had significantly higher one-year all-cause mortality and less frequent percutaneous coronary interventions compared to controls.	MI
Emilsson et al. [21]	2014	Sweden	Cohort study	Case: 29,096 celiac patients Control: 144,522 controls	Not specified	Not specified	Yes, there is an association between CD and an increased risk of IHD.	IHD
Emilsson et al. [20]	2012	Sweden	Population-based cohort study	Case: 29,071 individuals with CD Control: 144,429 reference individuals	Median age at study entry was 30 years (range 0-95)	Case: 18,001 (61.9%) Control: 89,526 (61.9%)	Yes, there was a moderately increased risk of idiopathic DCM in patients with CD (hazard ratio, 1.73; 95% confidence interval, 1.00 to 3.00), although the risk estimate failed to attain statistical significance (P = 0.052)	Idiopathic DCM
Ludvigsson et al. [22]	2011	Sweden	Population-based cohort study	Case: 28,190 individuals with CD Control: 229,800 reference individuals	Median age at study entry was 29 years for CD, 47 years for inflammation, and 35 years for latent CD.	Case: 17,655 (62.6%) females with CD Control: Not specified, but matched on age, sex, and calendar period	Yes, there was an increased risk of IHD in patients with CD.	MI and angina pectoris

Elfström et al. [19]	2007	Sweden	Population-based cohort study	Case: 9363 children and 4969 adults with CD Control: 69,851 age- and sex-matched reference individuals	Median Age at Diagnosis of CD: 2 years (range: 0-94 years). Myocarditis: 22.5 years for reference individuals, 78 years for CD patients3. Any Cardiomyopathy: 64 years for reference individuals, 62 years for CD patients. Pericarditis: 57 years for reference individuals, 54 years for CD patients. DCM: 76 years for reference individuals, 61.5 years for CD patients.	Case: 8431 (58.8%) Control: 41,188 (59.0%)	No association found between CD and later myocarditis, cardiomyopathy, or pericarditis.	Myocarditis, cardiomyopathy (any or dilated), and pericarditis
Wei et al. [23]	2007	UK and Ireland	Community-based cohort study	Case: 367 celiac patients Control: 5537 subjects with negative celiac immunology	Not specified	Case: 250 (68%) Control: 3620 (65%)	Yes, CD is associated with an increased risk of cardiovascular outcomes.	IHD, heart failure, cerebrovascular disease, cardiovascular death

Abbreviations: CD, Celiac Disease; CVD: Cardiovascular Disease; MI, Myocardial Infarction; IHD, Ischaemic Heart Disease; DCM, Dilated Cardiomyopathy.

Table 3. Quality assessment of included studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for case-control and cohort studies

Case-Control Studies

Author (Year)	Groups comparable aside from disease?	Cases and controls matched?	Same criteria for identification?	Exposure measured validly?	Exposure measured equally?	Confounders identified?	Strategies for confounders stated?	Outcomes assessed validly?	Exposure period sufficient?	Appropriate analysis used?
Dore et al. (2023) [28]	+	+	+	+	+	+	+	+	+	+

Cohort Studies

Author (Year)	Groups Similar and Recruited from Same Population?	Exposures Measured Similarly?	Exposure Measured Validly and Reliably?	Confounding Factors Identified?	Strategies for Confounding Stated?	Participants Free of Outcome at Start?	Outcomes Measured Validly and Reliably?	Follow-Up Time Sufficient?	Follow-Up Complete and Reasons for Loss Described?	Strategies for Incomplete Follow-Up Utilized?	Appropriate Statistical Analysis Used?
Conroy et al. (2022) [9]	+	+	+	+	+	+	+	+	+	+	+
Kårhus et al. (2020) [25]	+	+	+	+	+	+	+	+	+	+	+
Gajulapalli and Pattanshetty (2017) [11]	+	+	+	+	+	+	+	+	?	?	+
Emilsson et al. (2015) [14]	+	+	+	+	+	+	+	+	+	+	+
Emilsson et al. (2014) [21]	+	+	+	+	+	+	+	+	+	+	+
Emilsson et al. (2012) [20]	+	+	+	+	+	+	+	+	+	+	+
Ludvigsson et al. (2011) [22]	+	+	+	+	+	+	+	+	+	+	+
Elfström et al. (2007) [19]	+	+	+	+	+	+	+	+	+	+	+
Wei et al. (2007) [23]	+	+	+	+	+	+	+	+	+	*	+

This table summarizes the quality assessment of each study under various categories. Green plus signs (+) indicate a low risk of bias, red negative signs (-) indicate a high risk of bias, yellow question marks (?) indicate uncertainty in assessing bias risk, and blue asterisks (*) indicate situations in which assessment of bias is not applicable.

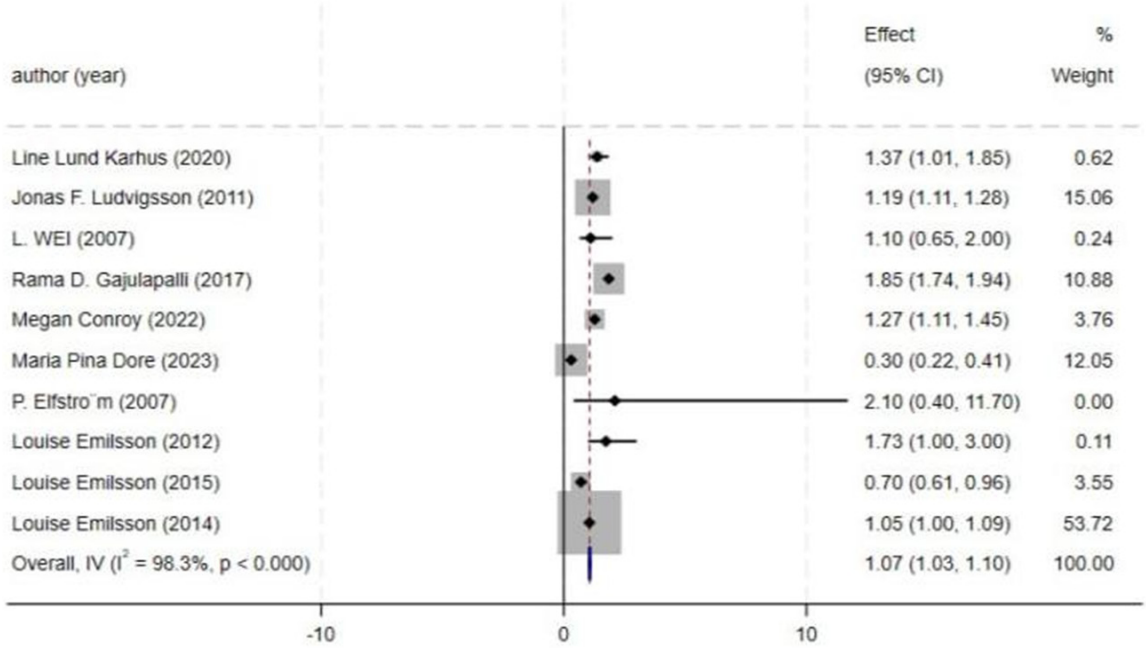

Figure 2. Forest plot of the association between celiac disease and cardiovascular disease risk. Abbreviation: CI, confidence interval.

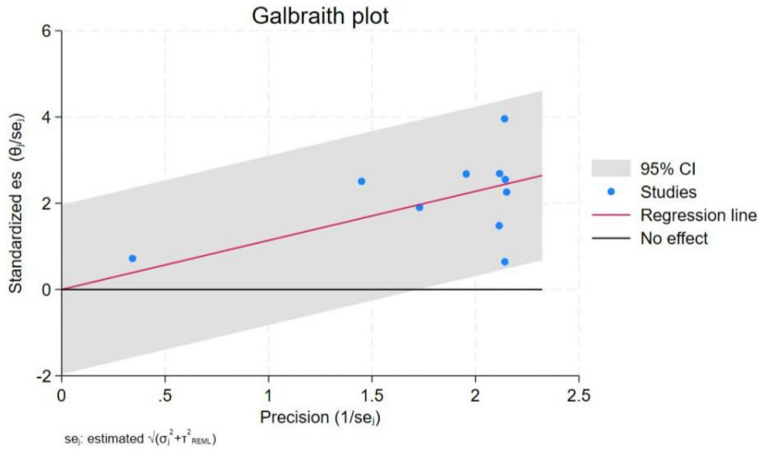

Figure 3. Galbraith plot of the association between celiac disease and cardiovascular disease risk. Abbreviation: CI, confidence interval.

population of 49,621,333 participants, represents a statistically significant 7% increased risk of CVD in patients with CD compared to controls, with a pooled adjusted OR of 1.07 and a 95% CI of 1.03-1.10. These result provides strong evidence supporting the association of CD and an increased risk of developing CVD, supporting the hypothesis that patients with CD have an increased risk for developing cardiovascular complications.

Comparison with previous research

Our meta-analysis results are consistent with several previous studies that have reported an association between CD and increased CVD risk. According to Ludvigsson et al. (2011), a nationwide cohort study in Sweden reported a 19% increased risk of coronary artery disease in patients with CD [22]. This is comparable to the higher risk estimate compared to our summary result. This could be because they focused on IHD and not CVD in general [22]. This discrepancy could indicate that some types of CVD, such as B. arteriosclerosis, are more closely related to CD than others.

Similarly, in a study, Gajulapalli and Pattanshetty (2017) reported an even stronger association with CAD prevalence, which was almost twice as high in CD patients compared to controls, with an OR of 2.09 and a 95% CI: 2.03-

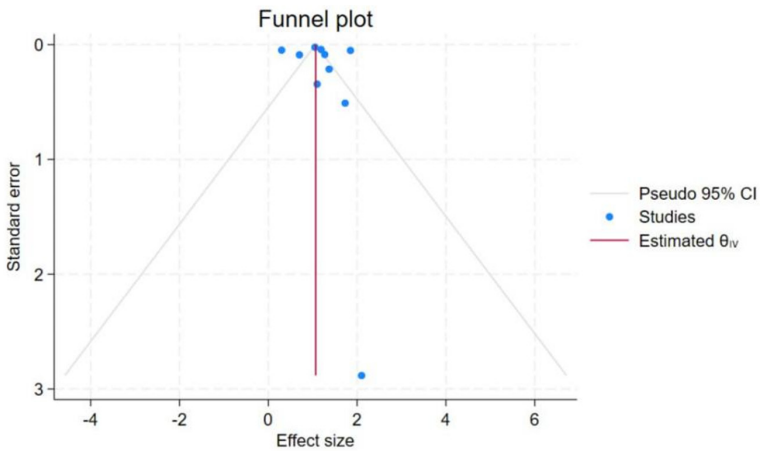

Figure 4. Funnel plot for publication bias assessment. Abbreviation: CI, confidence interval.

2.15 [11]. This may be explained by their focus in particular on CAD, which may have a closer association with CD than other forms of CVD. Therefore, with all due respect, this significant increase in the risk of CVD potentially highlights the potential impact that CD could have on coronary artery health and suggests that it would be justified to establish targeted screening for CVD in patients with CD.

On the other hand, not all studies were able to establish such clear connections and reported a lack of a strong association between CD and CVD. According to Huang's (2022) research, there is no direct link between CD and any of the following conditions: coronary heart disease, myocardial infarction, angina, atrial fibrillation, venous thromboembolism, large artery stroke, cardioembolic stroke, small vessel stroke, ischemic stroke, myocardial infarction and other forms of cardiovascular disease [26]. Similarly, Emilsson et al. (2012) studied first-degree relatives of patients with CD and found that the risk of coronary artery disease is only minimally increased, which is clinically quite insignificant [20]. This is particularly interesting because it means that CD itself may well be associated with an increased risk of CVD [13], but the genetic component of this association may be limited [27]. It questions the mechanisms behind the CD-CVD connection, which are likely related to environmental or immune-mediated factors rather than genetic factors.

Impact of gluten-free diet on CVD risk

Our results differ from those of Dore et al. (2017), which found that CD reduced the risk of CVD in terms of carotid artery lesions, with a greater benefit in subjects who were more adherent to a gluten-free diet in the long term [28]. In contrast, a study by Filardi et al. (2023) suggested that although a gluten-free diet may have a positive effect on the lipid profile in CD patients, its influence on cardiovascular risk factors remains unclear [29]. This inconsistency could be due to differences in the populations studied or in the CVD outcomes considered - or more generally, dietary interventions [12]. Their result thus indicates that strict adherence to a gluten-free diet may have some kind of protective effect in reducing the risk of CVD in CD patients. The effects of gluten-free diets are not taken directly in our study, but this conflicting evidence of association between gluten-free diets and cardiovascular health in CD patients points to the need for more research on the long-term cardiovascular outcomes in order of nutritional needs in CD patients.

Types of CVD affected by CD

The connection between CD and certain forms of CVD can be complex. While our meta-analysis showed an overall increased risk of CVD, some studies found no strong association between CD and inflammation-related CVD, such as Elfström et al. (2007) which reported no association between CD and inflammation-related CVD, including cardiomyopathy, pericarditis, and myocarditis, particularly in individuals diagnosed with CD in childhood [19]. This may suggest that the increased risk of CVD in CD patients may be due to certain types of CVD, such as atherosclerotic diseases, which could be higher than in inflammatory heart diseases. The reason for this could be that compared to healthy individuals, celiac patients have thicker carotid intima-media [30]. A study by Kårhus et al. (2018), conducted on a cohort

of 16,776 people, found a higher incidence of neoplasia and CVD in undiagnosed CD [25]. This result therefore highlights the need for diagnosis and treatment in the early stages of this disease, as it could impact not only cardiovascular outcomes in diagnosed patients but also in those in whom CD remained undetected, which this results strongly support our issue of association between CD and a increased risk of CVD comorbidities amphasizing the neoplasia.

As noted by Emilsson et al. (2012) examined the association between CD and dilated cardiomyopathy and a 73% increase in its incidence in patients with CD. In particular, this sharp increase in the risk of this disease, especially in the first year after diagnosis of CD, may indicate a link between these two diseases and certain forms of cardiomyopathy [20]. The temporal relationship described in this study may lead to questions as to whether the acute inflammatory processes at the time of initial diagnosis of CD contribute to acute cardiac complications. These findings have provided noticeable evidence that supports our result on the connection between CVD and CD. Our study highlighted a potential link between the inflammatory and immune-mediated processes associated with celiac disease and the increased risk of cardiovascular complications.

Cardiovascular mortality and age

Several researches also confirmed the relationship of CD and cardiovascular mortality and morbidities. The study by Naaraayan et al. (2021) also mentioned that CVD is associated with significant mortality in patients with CD [10]. Also, one more investigation by Ludvigsson et al. (2011) demonstrated that CVD is the leading cause of death in CD patients and especially an increasing risk of mortality for those diagnosed at the age of 60 and above 60 [22]. This age-related increase in cardiovascular mortality risk also makes cardiovascular monitoring and intervention urgent in older CD patients. These studies also support our result that indicates the relationship between ageing and the increasing risk of consequences of CVD in patients suffering from CD.

An interesting hypothesis by Brar et al. (2006) suggested a 40% reduction in mortality from ischemic heart disease in people diagnosed with CD who received gluten-free diets [31]. This argument is consistent with the findings of a study by Fousekis et al. (2020) [32]. The potential protective effect of gluten-free diets on cardiovascular outcome in CD patients, in contrast to our overall findings of increased cardiovascular risk, highlights the need for prospective research on the long-term cardiovascular effects of strict nutritional management in CD. In comparison to our result, in which the effects of gluten-free diets are not taken directly in our study, these findings underscore the need for further studies and investigations into the impact of dietary management on CVD consequences in those suffering from CD.

These different results in these studies point to the complexity of the relationship between CD and CVD. Modulation of this relationship by factors such as the specific type of CVD examined, age at diagnosis of CD, duration and adherence to gluten-free diets, and the presence of traditional cardiovascular risk factors is possible. Furthermore, conflicting results on the influence of gluten-free diets on CVD risk suggest that dietary treatment of CD may have effects other than gastrointestinal symptoms and may have both positive and negative effects on cardiovascular health, and The majority of these findings align with the results of our study and confirm that the finding, 7% increased risk in Cardiovascular Disease in individuals with Celiac Disease is greatly noticeable.

Strengths and limitations

One of the key strengths of this meta-analysis is that it represents an individually very large combined study population of more than 49 million participants, drawn from studies conducted in multiple countries. This large sample size provides tremendous statistical power and greatly improves generalizability. Our strict methodology further strengthens the reliability of the results: This includes a systematic search strategy, a careful quality assessment of the studies to be included, and thorough heterogeneity and bias assessments.

Nonetheless, it is important to note a few restrictions. First, variations in study design, populations, or outcome measures that could affect how our pooled estimate should be inter-

preted are probably the cause of the high heterogeneity of studies included in the meta-analysis (I^2 = 76 percent, P < 0.001). The results of our sensitivity analysis, which eliminated potential outliers, did not change significantly; However, this heterogeneity might suggest cautious interpretation of the data.

Second, most analyses were limited to observational studies that primarily used a cohort design. Although they cannot establish a cause-and-effect relationship between CD and CVD, these designs can provide important information about relationships. It is possible that different studies did not have the same ability to account for potential confounding factors such as diet, lifestyle, and other cardiovascular risk factors.

Finally, while some studies had indicated that the duration of CD or gluten-free diets may be significant moderating factors, our meta-analysis did not specifically look at these effects on the risk of CVD.

Clinical implications

Several clinical implications can be derived from the results of this meta-analysis. First, they point out that health professionals should be aware of the increased risk of CVD in a possible CD patient, even in the absence of traditional cardiovascular risk factors. This needs to be incorporated into comprehensive care strategies for patients with CD and could include more stringent cardiovascular screening and control of risk factors.

Given the controversial results of a gluten-free diet and the risk of CVD, dietary treatment of CD could have effects beyond gastrointestinal symptoms. This was not the direct aim of our meta-analysis; However, given these results, potential cardiovascular benefits from strict adherence to a gluten-free diet in patients with CD appear to be worthy of investigation and may have such implications for clinical practice.

Inflammatory heart disease remained undetectable in some studies associated with CD, suggesting that the risk of CVD may be better related to the atherosclerotic process, with preventive measures targeting atherosclerotic disease of CVD and other modifiable ones Target risk factors in patients with CD.

Future research

This meta-analysis raises several areas for future research. First, studies are needed that are prospectively designed to test the causal relationship between CD and CVD, going beyond association evidence from observational studies. Such a study should aim to elucidate the pathophysiological mechanisms linking CD to increased CVD risk.

Further research is needed on the effects of gluten-free diets on the risk of CVD in patients with CD. Therefore, the prospectively conducted studies on cardiovascular outcomes related to diet adherence and duration may prove more helpful in concluding clinical management.

Third, the search for genetic associations between CD and CVD risk could explain the variability of results in different studies and populations. This could be done in genome-wide association studies or targeted genetic analyses.

Finally, research into specific subtypes of CVD associated with CD could clarify which CVDs are most strongly associated with the presence of CD and then ultimately lead to more targeted prevention and screening strategies.

Conclusion

The present meta-analysis provides limited but notable evidence that individuals with CD have a higher risk of CVD. The results of this study suggest that much more research is needed to fully understand the complicated interactions between diseases and to devise the most effective plans to reduce the risk of CVD in CD patients, even if this affects the Those with this disease cardiovascular health.

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Disclosure of conflict of interest

None.

Abbreviations

CD, Celiac Disease; CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; PRISMA,

Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subject Headings; JBI, Joanna Briggs Institute; OR, Odds Ratio; CI, Confidence Interval.

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