

Alimentary Tract

Cardiovascular disease in patients with coeliac disease: A systematic review and meta-analysis

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ABSTRACT

Background: Coeliac disease has been associated with an increased risk of cardiovascular disease in some studies, whereas other studies have shown no association. We performed a systematic review and meta-analysis of cardiovascular disease in celiac disease.

Methods: Pubmed, Cinahl, EMBASE and Medline via Ovid were searched for relevant articles published until January 5, 2015. English-language articles on studies with more than 20 patients were included, and were quality rated using the GRADE risk of bias tool. We used random-effects models and assessed heterogeneity using the I^2 statistic.

Results: Ten studies were relevant, reporting the risk of myocardial infarction, cardiovascular death and stroke in 33,128/32,903/32,466 coeliac disease patients respectively. Only one study examined celiac disease and a composite measure of cardiovascular disease and this study found a hazard ratio of 1.10 (95%CI 1.03–1.28). In a meta-analysis, we observed an increased risk of stroke (OR 1.11; 95%CI 1.02–1.20). The risks of myocardial infarction (OR 1.12; 95%CI 0.83–1.40) and cardiovascular death (OR 1.12; 95%CI 0.96–1.29) were similar but were estimated with less certainty. Heterogeneity was low for all outcomes except for myocardial infarction where it was moderate.

Conclusion: Coeliac disease was associated with a modestly increased risk of cardiovascular disease, but the evidence base is limited.

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1. Introduction

Celiac disease (CD) is an immune-mediated disease characterized by villous atrophy and intestinal inflammation affecting approximately 1% of the population in the western world [1]. Inflammation and in particular elevated C-reactive protein (CRP) levels have been associated with an increased risk of atherosclerosis [2]. Several other diseases characterized by systemic inflammation, such as systemic lupus erythematosus [3] and rheumatoid arthritis [4], have been associated with an increased risk of atherosclerosis and cardiovascular mortality. The evidence for a link with cardiovascular disease (CVD) in CD is mixed, with positive associations seen in some studies [5] but not in all [6].

The aim of this study was to perform a systematic review of the evidence on the association of CD with CVD. We hypothesized that individuals with CD are at increased risk of CVD.

2. Methods

Our study review protocol is registered and available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006419

2.1. Search

We searched PubMed, EMBASE and Medline via Ovid and Cinahl for relevant articles published until 5th of January 2015 with the following search strategies:

1. ("celiac disease" OR "coeliac disease") AND (cardiovascular OR heart OR coronary OR stroke OR arrhythmia OR cardiac OR

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- cardio* OR vascular) NOT (truncus OR mesenteric OR “celiac axis” OR “coeliac axis” OR “celiac plexus” OR “coeliac plexus” OR “celiac artery” OR “coeliac artery”)
2. (“celiac disease” OR “coeliac disease”) AND (mortality) NOT (truncus OR mesenteric OR “celiac axis” OR “coeliac axis” OR “celiac plexus” OR “coeliac plexus” OR “celiac artery” OR “coeliac artery”).

The search was conducted by LE and revealed 3872 titles (of which some were duplicates) out of which 211 were deemed potentially relevant. Corresponding abstracts were then read by LE and JFL. In total 27 articles were read in full-length. None of the authors were contacted.

2.2. Study selection

We included case control or cohort studies comparing celiac patients to expected population rates via standardized morbidity ratios (SMR)/standardized incidence ratios (SIR) or matched controls reporting any of the following outcomes of interest: CVD death, non-fatal myocardial infarction (MI), non-fatal stroke, heart failure, or unstable angina requiring hospital admission. We excluded studies examining undiagnosed CD and CVD and studies with fewer than 20 patients. We also excluded studies where the results were not age- and sex-matched since the outcome is highly dependent on age and sex. The original search was not language-restricted but during the selection process we selected publications written in English only. There was no restriction concerning follow-up time or publication years. We also intended to collect secondary outcomes (hypertension, hypercholesterolemia, smoking, diabetes and obesity) if available, however this was not possible since it was rarely reported in the selected studies. Of the 27 articles read in full-length, 14 were relevant for the review. For some of the eligible articles participants overlapped partially e.g. several articles from Sweden, Italy and the UK overlapped since the populations reported were not mutually exclusive. For this reason we chose to keep the 10 most recent and largest publications for the main meta-analyses reported in this study. We used PRISMA guidelines for the reporting of studies and results [7].

The 10 relevant publications included in the systematic review are presented in Table 1. However, additional meta-analyses based on the 14 studies (and hence partial overlapping of individuals) were performed, but as the results were very similar to the meta-analyses based on non-overlapping results they were not reported. Apart from the issue of overlapping populations, all reasons for exclusion of the 17 articles are found in Supplementary Table S1 [28–41]. In total, 10 studies were included in the systematic review and 9 of them in any of the meta-analyses. In addition to the publications described above we also identified two conference abstracts where no full-text publication has yet been published [8,9] as well as a study on mortality that did not report sex-specific HR/OR for cardiovascular death [10]. These were not included in the review or meta-analyses but are commented on in Section 4. Data were extracted independently by LE and JFL and discrepancies were solved through consensus. In one of the studies the hazard ratios (HRs)/odds ratios (ORs) were reported separately for different exposure age groups [11]. In this case the non-overlapping results are presented separately (appearing as two studies) in graphs and tables.

2.3. Analysis

Since our search generated a mixture of studies where the risk of CVD was either calculated compared to controls or as SMR/SIR and as the outcome was rare we assumed that OR approximately equals

RR. Hence SMR, SIR, OH, RR and HRs were treated as equivalent measures of risk, as has been done previously [12]. We used random effects models using an inverse variance based method, as we a priori expected the true association to differ between populations. Potential publication bias was assessed by Egger's tests and Funnel plots [13]. Heterogeneity was assessed with the I^2 statistics. GRADE *risk of bias tool* was used to categorize study quality. We used Stata 13 for all analyses.

3. Results

Only one study reported an overall measure of any CVD (a composite measure of CVD death, non-fatal MI and non-fatal stroke) as a post hoc analysis, this study found a HR of 1.10 (95%CI = 1.03–1.28) [5], heart failure and unstable angina requiring hospital admission was not included in this overall measure. Since it was the only study that reported an overall composite measure we included it in the systematic review but did not assess this measure (“any CVD”) in a meta-analysis. In total 6 studies reported a risk estimate for MI; four studies [5,6,14,15] reporting in total 33,128 patients were included in our main analysis whereas two [16,17] with partial overlap were excluded. Eight studies reported risk estimates for CVD death, of whom six [5,14,18–21] including 32,903 patients were included in our main analysis and two [17,22] were excluded due to partial overlap. Stroke data were reported in three studies; two [6,23] were included involving 32,466 patients and one [16] was excluded due to partial overlap. Only one study reported the outcome of heart failure [16] and two studies reported data on angina [5,16]; however, they were both from Sweden and consisted of partially overlapping populations. Due to the lack of study data we did not perform any meta-analyses on heart failure and angina but instead report the data of the original studies. The included studies originated from Sweden, UK, Italy and Finland. In general the number of studies per outcome was small and testing for heterogeneity showed $I^2 = 64\%$ e.g. moderate for the MI meta-analysis and $I^2 = 9\%$ e.g. low for the CVD death meta-analysis. With few studies and low heterogeneity we did not attempt to further explore the heterogeneity. Eggers test and funnel plots were not performed since we identified less than 10 studies [24]. All of the included studies were categorized as of low quality in the GRADE scoring system.

3.1. Components of cardiovascular disease

We found an increased risk of stroke (OR=1.11; 95%CI=1.02–1.20; based on 2 studies), the estimate was heavily influenced by the largest study [23] (Fig. 3). Similar estimates were also found for MI (OR=1.12; 95%CI=0.83–1.40) (Fig. 1) and death from CVD (OR=1.12; 95%CI=0.96–1.29) (Fig. 2) although the CIs of these estimates were wider and hence did not attain statistical significance. For the outcome of heart failure, no meta-analysis was performed since only one study reported this outcome in CD. That study [16] showed an increased risk OR=1.41 (95%CI=1.22–1.62) when comparing CD inpatients to general population controls; however, when comparing with controls who had at least one record in the inpatient registry no association was detected. There were two studies reporting of angina pectoris but both were from Sweden and partially overlapping and hence we performed no meta-analysis for this outcome. Both showed an increased risk HR=1.27; (95%CI=1.07–1.51) [5] and HR=1.46; (95%CI=1.25–1.70) [16]. As was the case for heart failure, the latter study did not show a significant association when restricting *controls* to individuals with an inpatient diagnosis.

Table 1
Cardiovascular disease in coeliac disease patients: included studies.

Title	Publication year	Country	Years	CD patients	Age at CD diagnosis	Inclusion criteria	Grade score	Effect measure and adjustments
Anderson [18]	2007	Northern Ireland, UK	1993–1996, follow-up until 2003, December 31	490	Mean 45 years (range 0–91 years)	IgA EMA and/or IgA AGA Belfast	Low	SIR
Corrao [19]	2001	Italy	1962–1994	1072	Mean: 35.7 years	Biopsy-proven CD from 11 gastroenterology units	Low	SMR
Grainge ^a [20]	2010	UK	1958 until 2006, (prevalent cases before 1978)	1285	45.6 years	Celiac diagnosis based on biopsy at 2 district general hospitals in Derby	Low	SMR
Ludvigsson # [16]	2007	Sweden	1964–2003	13,358	Median: 2 years	Inpatients with relevant ICD codes (celiac disease)	Low	HR, inpatient control matched by sex and age
Ludvigsson [5]	2011	Sweden	1969–2007	28,190	Median: 29 (0–95 is range)	Villous atrophy at one of 28 pathology labs	Low	HR, age, sex, county and calendar year matched controls
Ludvigsson [23]	2012	Sweden	1969–2007	28,676	Median: 30	Villous atrophy at one of 28 pathology labs	Low	HR, age, sex, county and calendar year matched controls
Solaymani Dodaran [21]	2007	UK Lothian region	1961–2004	625	Median: 24.1	Attended certain hospitals in Lothian region in Scotland. Pathology data + hospital data on celiac disease + local branch of celiac society	Low	SMR
Wei [15]	2008	UK, Scotland	1993–2003	367	46 years	Either biopsy-verified CD or EmA+	Low	HR, All individuals testing negative for AEA-IgA in the same laboratory. Outcome measure adjusted for age, gender, social deprivation, diabetes mellitus, any cardiovascular drug use, folic acid, gluten-free prescriptions, allopurinol, HRT, NSAIDs and oral glucocorticoids
West [6]	2004	UK	1987–2002	3790	No data	>25 years with a diagnosis of CD in the GPRD database	Low	HR, control from general population matched on sex, age and general practice and follow-up-time
Viljamaa [14]	2006	Finland, Tampere	1960–2000	781	39	CD patients diagnosed at Tampere university hospital area 1960–2000	Low	SMR

^a Analysis stratified by 1–2 and >2 years after diagnosis. # Partial overlap with Ludvigsson (2011), hence not included in meta-analyses but systematic review concerning reported angina and heart failure. AEA-IgA, anti-antomyseal antibodies of IgA type; CD, celiac disease; HR, hazard ratio; SIR, standardized incidence ratio; SMR standardized morbidity ratio.

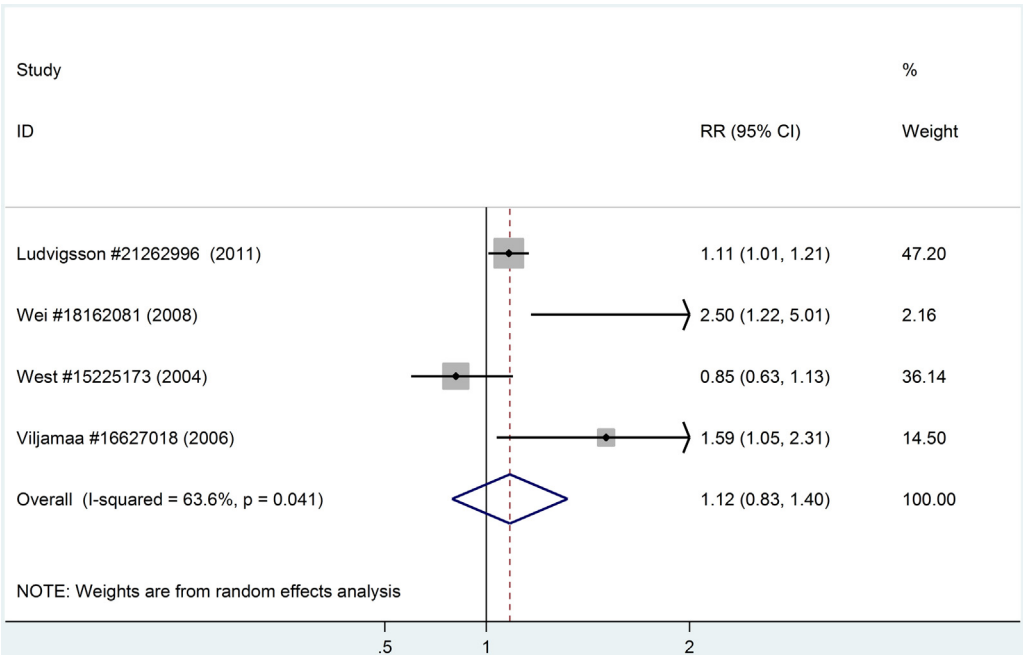


Fig. 1. Forest plot myocardial infarction in celiac disease. # is followed by PMID (PubMed Indexed) number.

4. Discussion

We reviewed over 3800 abstracts and in the end identified fourteen studies that were relevant for our systematic review on CD and CVD. Due to partial overlap of subjects (patients and/or controls), 10 of these 14 studies were included in our systematic review and 9 of them in our meta-analyses. Only one study reported “any CVD” in CD [5] as a composite outcome and that study found a 10% increased risk, consistent with data on other outcome measures in our meta-analyses (MI, death from CVD and stroke). These associations attained statistical significance for stroke but not for

the other outcomes, most likely due to lack of power for some of the disease specific analyses. On the contrary to our findings a recent study from the UK [10] showed a crude decrease in CVD death in CD patients compared to controls, however there was a different sex distribution in CD patients (34.9% males) compared to controls (48.9% males) that probably explains the rather lower numbers in crude CVD deaths. The lack of age- and sex-adjusted data was the reason for not including this study in our systematic review. Still that paper demonstrated a lower excess cumulative incidence of CVD death in CD patients (−0.08%; 95%CI = −0.13 to −0.04) when adjusting for competing risks, socioeconomic status,

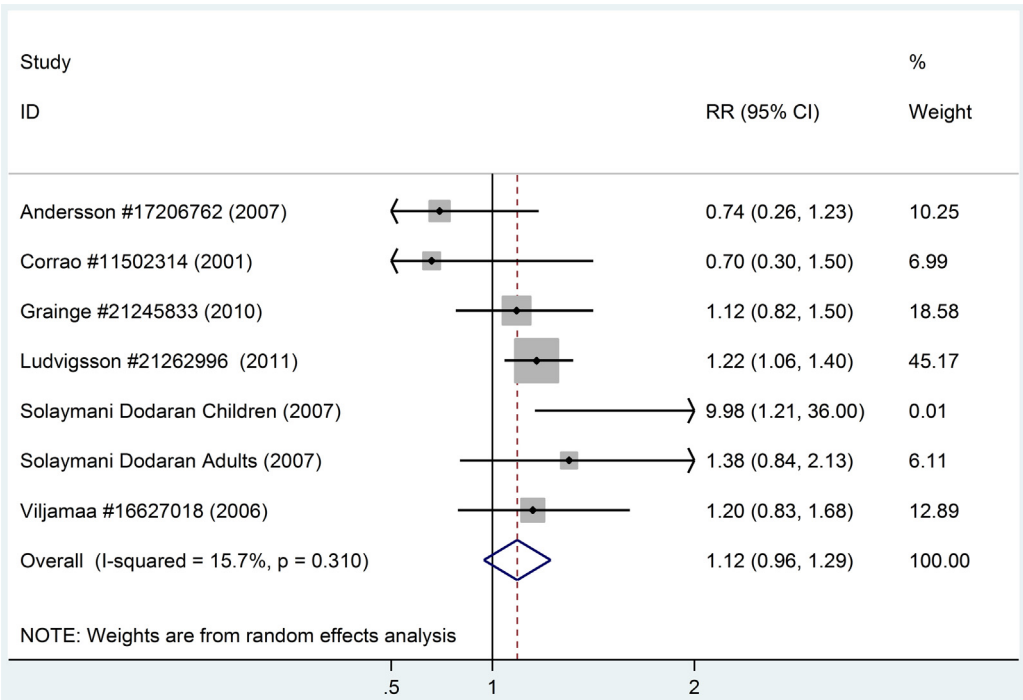


Fig. 2. Forest plot cardiovascular death in celiac disease. * PMID (PubMed Indexed) for this article is 17324126. # is followed by PMID number.

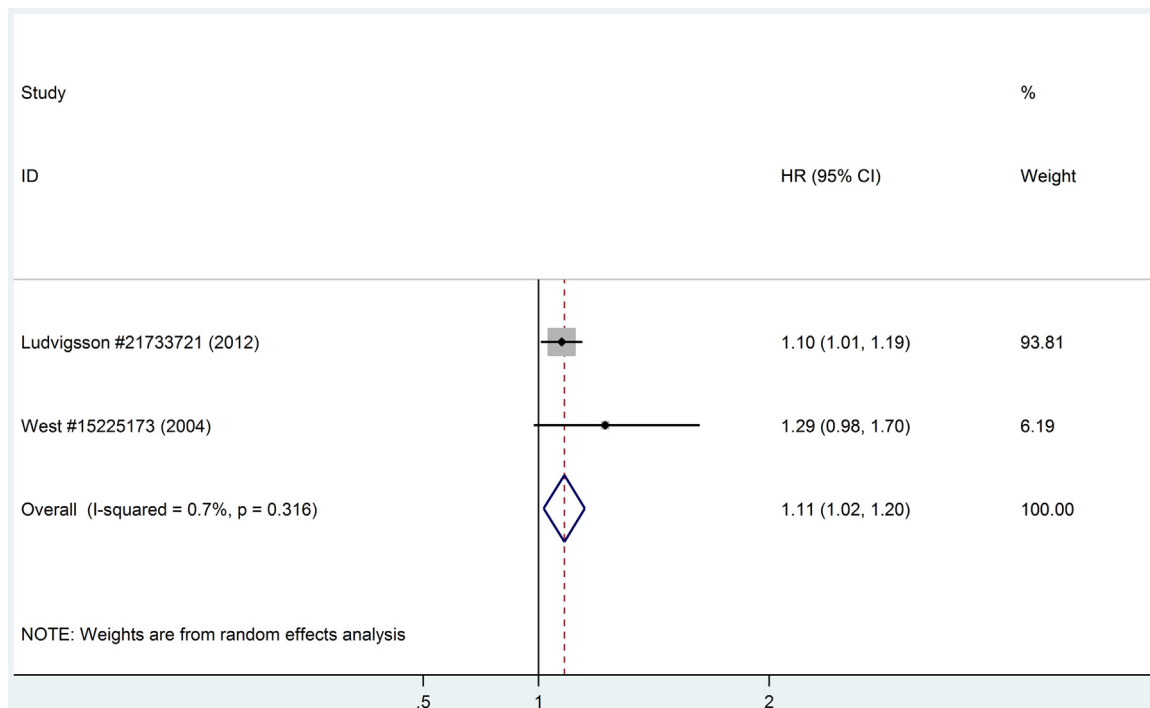


Fig. 3. Forest plot stroke in celiac disease. # is followed by PMID (PubMed Indexed) number.

age and gender. Although not included in the meta-analysis these small changes would not likely have impacted our overall estimates had the British data [10] been included. In contrast one of the excluded abstracts showed a twofold increased risk of coronary artery disease in American CD patients [9]. All in all a 10% increased risk of CVD is probably reasonable given all the published evidence.

The excess risk of each component of the CVD outcome in our meta-analyses was smaller than suggested by some earlier studies [15]. The few studies reporting on angina and heart failure showed about 30–40% increased risk when compared to general population controls but no increased risk compared to controls with at least one inpatient registration. Hence these estimates are probably to a greater extent inflated by ascertainment bias and therefore less reliable than the ones included in our meta-analyses. Studies of morbidity in patients after a diagnosis of CD are prone to ascertainment bias, since a large proportion of patients with CD remain undiagnosed [25]. As such, patients who are diagnosed with CD may be different in important ways compared to those who remain undiagnosed.

4.1. Strengths and limitations

Strengths of this study include its registered protocol, systematic review of the literature, and close review of included publications so as to assure that CD subjects and controls were not counted more than once, given the overlap of populations in these studies. Additional strengths include the secondary meta-analyses of each component for the composite outcome of CVD. Limitations include the low number of included publications, in particular regarding the composite outcome of CVD, which was measured in only one study. We suggest that composite CVD outcomes should be reported in future publications on the subject. Another consequence of the limited number of included studies is that the authors of this meta-analysis themselves performed several of the included and high-weighted studies. This might introduce academic bias, however no relevant studies were excluded, and the importance

and direction of this potential bias is unknown. Another limitation to the analyses of the outcome MI is that we identified moderate heterogeneity, but due to small number of included studies we were not able to assess the reasons any further. It would also be important to perform studies reporting on this composite outcome in the future, given the major burden of morbidity and mortality worldwide and given significant improvement of prevention strategies in recent decades. Generalizability is also a potential limitation; all included studies originated from Europe, and accordingly this systematic review is reflecting the association in a European setting only. Applicability to patients with CD in the United States [26] or the developing world [27] is uncertain. However, two American abstracts not yet available in full-text indicate that there is an increased risk of CVD in CD patients also in America [8,9]. Further publications on the association in other countries and continents would be desirable to establish if the risk of CVD is indeed increased in CD patients in general.

An additional limitation to this study is that we did not include papers written in other languages than English. We are however not aware that any of the screened abstracts (in English) where the original article was in a different language included any data on celiac CVD associations. Of note, all of the included studies were published after year 2000 and the spectrum of CD diagnostics and symptoms has changed over the last decades with the introduction of serologic markers. Finally, it remains unclear whether the timing of CD diagnosis impacts CVD risk. The identified studies for this systematic review did not allow us to assess if CD diagnosed in childhood, in comparison to those diagnosed in adulthood, are more prone to be diagnosed with CVD. Another limitation is that we did not include unpublished data as we did not contact the authors.

In this meta-analysis and systematic review of the literature, CD was associated with a 10% increased risk of CVD as a composite outcome and for stroke in particular. Estimates for MI and CVD death were similar but did not attain statistical significance. Future studies should investigate the impact of timing of diagnosis and other clinical features on cardiovascular outcomes.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dld.2015.06.004>

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