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META-ANALYSIS

# Associations of coeliac disease with coronary heart disease and cerebrovascular disease: A systematic review and meta-analysis

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**Abstract** *Aims:* Clinical experience suggests that atherosclerotic disease is common in individuals with coeliac disease, but epidemiological studies have had contradicting findings. To summarise the currently available evidence, we systematically reviewed and analysed observational studies of the association of coeliac disease or dermatitis herpetiformis with coronary heart disease (CHD) or stroke.
*Data synthesis:* We searched for studies comparing CHD or stroke outcomes with individuals with and without coeliac disease or dermatitis herpetiformis. Three investigators independently searched electronic databases, identified relevant studies and extracted data. Study-specific results were combined in random-effects meta-analyses, and heterogeneity was quantified using the $I^2$ statistic and meta-regression. Twenty-one studies were included in our systematic review and 18 in the meta-analyses. For CHD, the pooled hazard ratio for incident disease was 1.05 (95% confidence interval (CI): 0.93, 1.19) and the overall standardised mortality ratio was 1.21 (0.99, 1.49). For stroke and brain haemorrhage, the corresponding estimates were 1.10 (95% CI: 1.00, 1.21) and 1.43 (0.97, 2.10), respectively. There was moderate to considerable heterogeneity among the study-specific estimates. In addition, many estimates were based on small numbers of outcomes and they had limitations in terms of adjustment for potential confounders.
*Conclusion:* Our meta-analyses lend some support to an association between coeliac disease and CHD or cerebrovascular disease, but the evidence base was heterogeneous and had limitations. Our systematic review highlighted a need in this area for adequately powered prospective studies with appropriate adjustment for potentially confounding factors.


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## Introduction

Coeliac disease and dermatitis herpetiformis (a skin manifestation of coeliac disease) are autoimmune-mediated illnesses, triggered in genetically susceptible individuals by the ingestion of gluten, the storage protein in wheat, rye and barley [1]. Coeliac disease was considered to be a rare childhood disorder for a long time, but recent population-based screening studies have shown that it can be diagnosed at any age [2] and that it is more common than previously thought, with a prevalence varying from 1% to 2% in the developed world [1,3–6].

It is biologically plausible that coeliac disease could be associated with the risk of coronary heart disease (CHD) and stroke. Tissue transglutaminase (tTG), the main autoantigen in coeliac disease, can enhance angiogenesis, whereas antibodies against tTG have the ability to inhibit angiogenesis [7–9]. Moreover, patients following a gluten-free diet do not always eat a healthy balance of fats, carbohydrates and fibre [10–12], which could contribute to the pathogenesis of atherosclerotic disease. On the other hand, it is also possible that coeliac disease, particularly when untreated, leads to malabsorption of nutrients in the small intestine and consequently low lipid and cholesterol concentrations, thus lowering the risk of cardiovascular events [13]. Findings from a study comparing ischaemic heart disease risk factors in participants with and without coeliac disease exemplify these contradicting observations: patients with coeliac disease were less likely to smoke and had, on average, lower body mass index and blood cholesterol, but their blood pressure and circulating concentrations of C-reactive protein were similar to those of the comparison group [14].

The association of coeliac disease with atherosclerotic disease has been examined in a number of observational studies. However, these have had inconsistent findings, with positive, negative and null associations reported [15–35]. To the best of our knowledge, this literature has not been comprehensively reviewed before. We have conducted a systematic review and meta-analyses of observational epidemiological studies of the associations of coeliac disease and dermatitis herpetiformis with CHD and stroke.

## Methods

### *Data sources and searches*

Details of our systematic searches are provided in Appendix 1. Briefly, we searched PubMed, Scopus, Web of Science and Cochrane Library from the inception of each database through to December 2014 for articles describing observational epidemiological studies of any design, and written in any language, using the keywords 'coeliac disease' and 'dermatitis herpetiformis' to define the exposure, and 'heart diseases', 'vascular diseases' or 'myocardial infarction', 'angina pectoris' or 'stroke' to define the outcome (Appendix 1). We included studies that compared individuals with coeliac disease or dermatitis herpetiformis with participants free of these disease or with a standard population. Studies of irrelevant exposures and outcomes were excluded. Where more than one article had been published using the same data, we included all publications in our systematic review, but we included only the estimates that were based on the largest number of participants or the longest period of follow-up in the meta-analyses. Three investigators (KH, OAK and AA) independently reviewed titles, abstracts and, where necessary, full-text articles and extracted data using a standard data extraction form. Where unadjusted and adjusted estimates were reported, the latter were extracted.

### *Data synthesis and analysis*

The main summary measures were hazard ratios (HRs) for incident disease outcomes and standardised mortality ratios (SMRs) for death outcomes. We used Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) to assess the risk of bias in individual studies [36]. Study-specific association estimates were pooled in random-effects meta-analyses [37], with heterogeneity being quantified using the $I^2$ statistic. We investigated small study effects using funnel plots and Egger's test for funnel plot asymmetry [38]. Potential sources of heterogeneity were explored using meta-regression [39]. Our main analyses were conducted using a DerSimonian and Laird estimator for between-study variance. We also explored the sensitivity of our findings to uncertainty about between-study variance using a Knapp–Hartung variance estimator [40,41]. Stata versions 12 and 13 were used for the analyses (Stata Corporation, College Station, TX, USA).

## Results

### *Systematic search results*

Of 3051 citations identified, 21 articles contained estimates of associations between coeliac disease or dermatitis herpetiformis and the prevalence, incidence or mortality of CHD, stroke or other cerebrovascular disease [15–35] (Fig. S1, Appendix 1). Details of these are provided in Table 1 (studies of diagnosed coeliac disease) and 2 (studies of unrecognised coeliac disease).

Of the 21 studies we reviewed, 13 studies were included in our meta-analyses [17,19,20,23–27,29–32,35] and eight in a narrative synthesis [17,19,20,25,27,30,31,35]. One study was excluded due to concerns over participant selection and missing data [34] and another because a more recent analysis of the same data was published and included [21] (Table 1). As the studies of unrecognised coeliac disease had different designs, exposures and outcomes, their findings were not pooled and were described narratively instead. Among the included articles, two [16,20] described analyses that were based on partly the same participants as previous publications [33,35]. For each pair of articles, the estimates based on the largest number of participants or the longest period of follow-up