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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

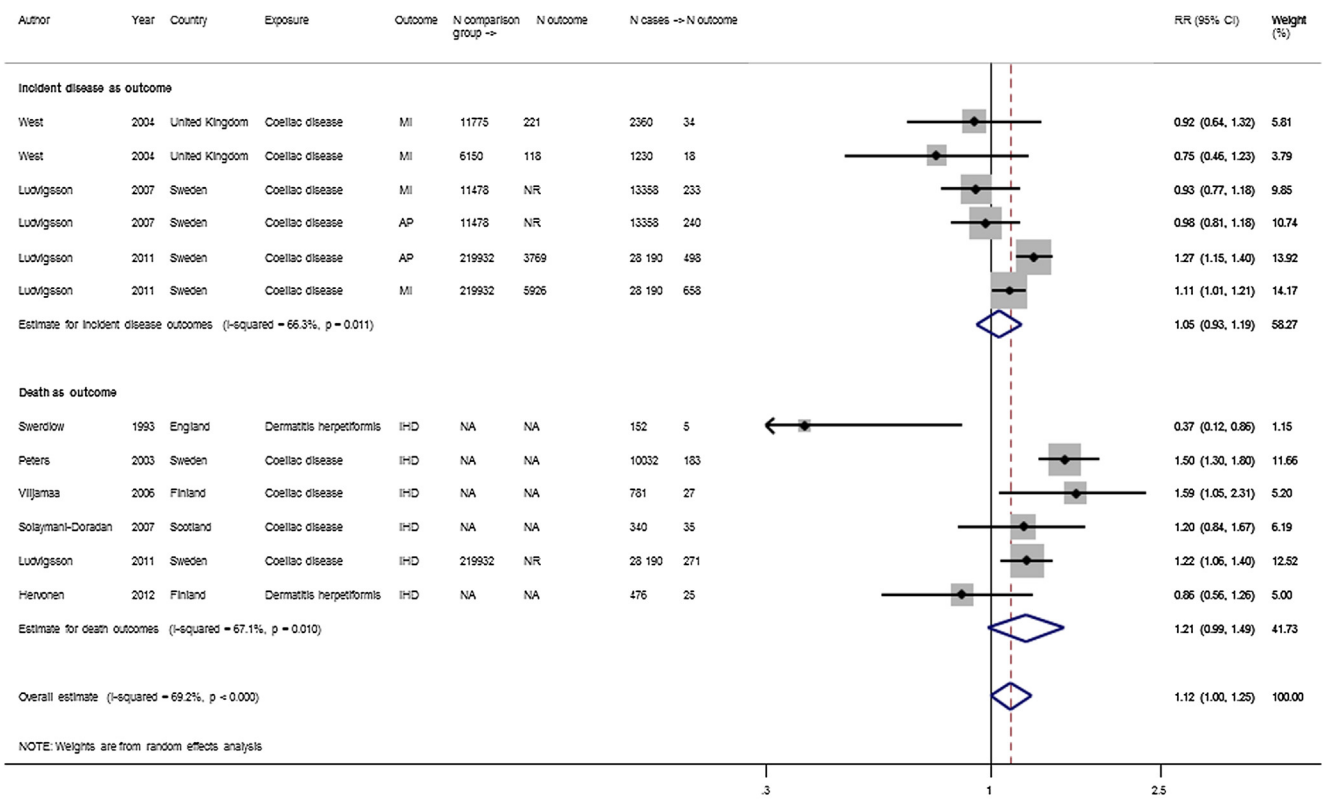
The main summary measures were hazard ratios (HRs) for incident disease outcomes and standardised mortality ratios (SMRs) for death outcomes. We used Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) to assess the risk of bias in individual studies [36]. 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

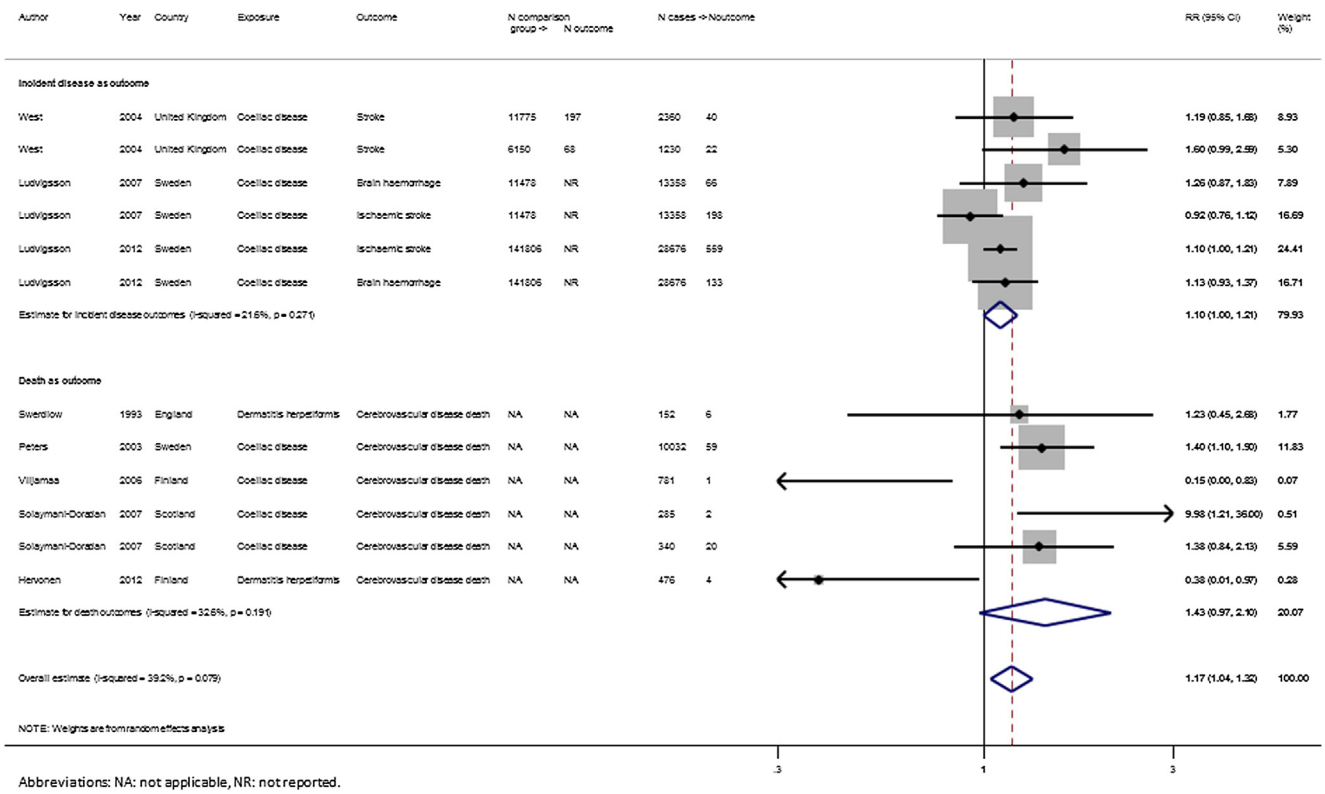
Of 3051 citations identified, 21 articles contained estimates of associations between coeliac disease or dermatitis herpetiformis and the prevalence, incidence or mortality of CHD, stroke or other cerebrovascular disease [15–35] (Fig. S1, Appendix 1). Details of these are provided in Table 1 (studies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



Abbreviations: MI: myocardial infarction; AP: angina pectoris; IHD: ischaemic heart disease; NR: not reported; NA: not applicable.

Figure 1 Associations of coeliac disease with coronary heart disease.



Abbreviations: NA: not applicable, NR: not reported.

Figure 2 Associations of coeliac disease with cerebrovascular disease or stroke.

Table 1 Summary of studies of clinically diagnosed coeliac disease and ischaemic cardiovascular disease.

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participant age and sex	Main findings	Comments	Risk of bias
Whorwell, 1976 [34] Case–control	Membership of Coeliac Society in England or Wales	Cause of death from a national death register	Coeliac disease: 77 IHD death: 9	**Age**: Not reported. **Women**: 45.5%	**Ratio of observed to expected**: Deaths from IHD: 0.45	Observed number of deaths compared to expected numbers, taking age, sex and calendar period into account. Coeliac disease cases were a mix of untreated individuals and those on gluten-free diet. Coeliac disease was self-reported. Outcome data were obtained for 55% of those whose relatives had informed the Coeliac Society about the participant's death.	Confounding: serious risk. Selection of participants: moderate risk. Measurement of exposure: serious risk. Missing data: critical risk. Measurement of outcomes: moderate risk. Overall bias: critical risk
Logan, 1989 [21] Case–control	Diagnosis of coeliac disease from local hospital records or patients identified through general practices or the local branch of the Celiac Society	IHD or cerebrovascular disease death from a national death register	Coeliac disease: 653 IHD death: 16 Cerebrovascular disease death: 11	**Age**: Not reported. **Women**: Coeliac disease cases: 60.0%	**Ratio of observed to expected**: Death from IHD: 0.9 Death from cerebrovascular disease: 1.2	Observed and expected mortality rates were calculated by age and sex. Based on the same data as the study by Solaymani-Doradan and colleagues, 2007.	Confounding: serious risk. Selection of participants: moderate risk. Measurement of exposure: low risk. Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Swerdlow, 1993 [30] Prospective case–control	Dermatitis herpetiformis from local hospital register	IHD or cerebrovascular disease from national death register	Dermatitis herpetiformis: 152 Ischaemic heart disease death: 5 Death from cerebrovascular disease: 6 Death from circulatory system disease: 14	**Age range**: <30–50+ **Women**: 30.3%	**SMR (95% CI)**: IHD: 0.37 (0.12, 0.86) Cerebrovascular disease: 1.23 (0.45, 2.68) Circulatory system disease: 0.63 (0.34, 1.06)	Standardised for age, sex and calendar year. Individuals with dermatitis herpetiformis had been on gluten-free diet.	Confounding: serious risk. Selection of participants: moderate risk. Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

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Table 1 (*continued*)

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participant age and sex	Main findings	Comments	Risk of bias
Corrao, 2001 [17] Prospective case–control	Biopsy-verified coeliac disease	Death register record of circulatory system disease	Coeliac disease: 1072 Circulatory system disease death: 7	**Mean (SD age)**: 35.7 (14.1) **Women**: 76%	**SMR (95% CI)**: Circulatory system disease: 0.7 (0.3, 1.5)	Standardised for age, sex and calendar year. Coeliac disease cases were a mix of untreated individuals and those on gluten-free diet.	Confounding: serious risk. Selection of participants: moderate risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Peters, 2003 [27] Prospective case–control	Coeliac disease from national hospitalisation register	IHD or cerebrovascular disease from national death register	Coeliac disease: 10,032 IHD death: 183 Death from cerebrovascular disease: 59 Death from circulatory system disease: 326	**Age range**: 0–70+ **Women**: 58.4%	**SMR (95% CI)**: IHD: 1.5 (1.3, 1.8) Cerebrovascular disease: 1.4 (1.1, 1.9) Circulatory system disease: 1.6 (1.4, 1.8)	Standardised for age, sex and calendar year. No details of gluten-free diet provided. Follow-up started 12 months after the discharge from the index hospitalisation (for coeliac disease).	Confounding: serious risk. Selection of participants: moderate risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
West, 2004 [32] Prospective case–control	Coeliac disease from primary care research database	MI or stroke from primary care research database	Coeliac disease: 2360 Controls: 11,775 **All**: *Coeliac disease*: MI: 52 Stroke: 62 *Controls*: MI: 339 Stroke: 265 **With prevalent disease**: *Coeliac disease*: MI: 34 Stroke: 40 *Controls*: MI: 221 Stroke: 197 **With incident disease**: *Coeliac disease*: MI: 18 Stroke: 22 *Controls*:	**Age range**: <35 to >75 **Women**: Coeliac disease: 68.6% Controls: 68.5%	**HR (95% CI)**: **Cases with prevalent coeliac disease**: MI: 0.92 (0.64, 1.32) Stroke: 1.19 (0.85, 1.68) **Cases with incident coeliac disease**: MI: 0.75 (0.46, 1.23) Stroke: 1.60 (0.99, 2.59)	Controls matched for age, sex, general practice and follow-up time. No details of gluten-free diet provided.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

			MI: 118 Stroke: 68				
Viljamaa, 2006 [35] Prospective case–control	Biopsy-verified coeliac disease or dermatitis herpetiformis	IHD or cerebrovascular disease from national death register	Coeliac disease: 781 Dermatitis herpetiformis: 366 **Coeliac disease**: Ischaemic heart disease death: 27 Cerebrovascular disease death: 1 Circulatory system disease: 34 **Dermatitis herpetiformis**: Ischaemic heart disease death: 13 Cerebrovascular disease death: 3 Circulatory system disease: 21	**Median (range) age**: Coeliac disease: 39 (1–84) Dermatitis herpetiformis: 38 (5–84) **Women**: Coeliac disease: 68% Dermatitis herpetiformis: 48%	**SMR (95% CI)**: **IHD**: Coeliac disease: 1.59 (1.05, 2.31) Dermatitis herpetiformis: 0.72 (0.38, 1.23) **Cerebrovascular disease**: Coeliac disease: 0.15 (0.00, 0.839 Dermatitis herpetiformis: (0.46 (0.10, 1.35) **Circulatory system disease**: Coeliac disease: 1.20 (0.83, 1.68) Dermatitis herpetiformis: 0.72 (0.44, 1.09)	Standardised for age, sex and calendar period. No details of gluten-free diet provided. Partially the same data as Hervonen and colleagues, 2012.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Solaymani-Dodaran, 2007 [29] Prospective case–control	Diagnosis of coeliac disease from local hospital records or patients identified through general practices or a coeliac society	IHD or cerebrovascular disease death from a national death register	Coeliac disease diagnosed aged <15: 285 Coeliac disease diagnosed aged ≥15: 340 IHD death: 35 Cerebrovascular disease death: 22	**Mean (median) age**: Coeliac disease diagnosed aged <15: 3 (1.5) Coeliac disease diagnosed aged ≥15: (45.4 (46.3) **Women**: Coeliac disease diagnosed aged <15:54.7 Coeliac disease diagnosed aged ≥15: 63.8	**SMR (95% CI)**: **IHD**: Coeliac disease diagnosed aged <15: - Coeliac disease diagnosed aged ≥15: 1.20 (0.84, 1.67) **Cerebrovascular disease**: Coeliac disease diagnosed aged <15: 9.98 (0.12, 36.0) Coeliac disease diagnosed aged ≥15: 1.38 (0.84, 2.13)	Standardised for age, sex and calendar year. No details of gluten-free diet provided.	Confounding: serious risk. Selection of participants: moderate risk Measurement of exposure: low risk Missing data: no information Measurement of outcomes: moderate risk Overall bias: serious risk
Ludvigsson, 2007 [23] Prospective case–control	Coeliac disease from national hospitalisation register	MI, AP, heart failure, brain haemorrhage or ischaemic stroke from national hospitalisation register	Coeliac disease: 13,358 Controls: 64,118 **Coeliac disease**: MI: 233 AP:240 Brain haemorrhage: 66 Ischaemic stroke: 198 Heart failure: 300	**Median (range) age**: 2 (0–94) Women: Coeliac disease: 59.3% Controls: 59.5 %	**HR (95% CI)**: MI: 0.93 (0.77, 1.18) AP: 0.98 (0.81, 1.18) Brain haemorrhage: 11.26 (0.87, 1.83) Ischaemic stroke: 0.92 (0.76, 1.12) Heart failure: 0.79 (0.68, 0.92)	Controls were matched for age and sex. Models were stratified for age, sex, county and calendar year. Controls were inpatients hospitalised for illnesses other than coeliac disease.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk

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Table 1 (*continued*)

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participant age and sex	Main findings	Comments	Risk of bias
			Controls: MI: 1032 AP: 934 Brain haemorrhage: 232 Ischaemic stroke: 842 Heart failure: 1228			No details of gluten-free diet provided.	Overall bias: serious risk
Wei, 2008 [31] Prospective case–control	Biopsy-verified or serologically verified coeliac disease	Hospitalisation or death record of cardiovascular disease (myocardial infarction, angina pectoris, stroke, transient ischaemic attack, congestive cardiac failure or cardiovascular death)	Coeliac disease: 185 Controls: 5181 *N* outcomes not reported for the subgroup in the analyses cited here.	Age range: <10–80+ Age not reported specifically for the subgroup in the analyses cited here. Women: coeliac disease: 68% Controls: 65%	**HR (95% CI)**: Cardiovascular disease: 2.50 (1.22, 5.01)	Adjusted for age, sex, area deprivation index, diabetes, CVD medication, folic acid intake, gluten-free food stuff prescriptions, allopurinol, HRT, NSAIDs and oral glucocorticoids. Controls were patients who had a negative coeliac disease test in the same laboratory. Coeliac disease cases were a mix of untreated individuals and those on gluten-free diet.	Confounding: moderate risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: no information Measurement of outcomes: moderate risk Overall bias: moderate risk
Ludvigsson, 2009 [25] Prospective case–control	Biopsy-verified coeliac disease or seropositivity for coeliac disease autoantibodies	Cardiovascular death from national death register.	Coeliac disease: 29,096 Seropositive: 3719 Controls: 228,632 **Cardiovascular deaths**: Coeliac disease: 1007 Controls: 9295	**Median (range) age**: Coeliac disease: 30 (0–95) Controls: not reported (age-matched) **Women**: Coeliac disease: 61.9% Controls: not reported (sex-matched)	**HR (95% CI)**: **Cardiovascular death**: Coeliac disease: 1.19 (1.11, 1.28)	Controls were matched for age, sex, county and calendar period. Models were stratified for age, sex, county and calendar period. Control group included some individuals with unrecognised coeliac disease: their follow-up ended at their date of coeliac disease diagnosis. This study is also described in Table 2.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Grainge, 2011 [19] Prospective case–control	Biopsy-verified or serologically verified diagnosis of coeliac disease	Cardiovascular death from a national death register	Coeliac disease: 1092 Cardiovascular deaths: 45	**Mean (SD age)**: 44.8 (19.1) **Women**: 8.5%	**SMR (95% CI)**: **Cardiovascular death**: *2+ years after coeliac*	Standardised for age and sex. No details of gluten-free diet provided.	Confounding: serious risk. Selection of participants:

					disease diagnosis: 1.12 (0.82, 1.50) *<2 years after coeliac disease diagnosis*: 0.42 (0.11, 1.07)		moderate risk Measurement of exposure: low risk Missing data: moderate risk Measurement of outcomes: moderate risk Overall bias: serious risk
Ludvigsson, 2011 [24] Prospective case–control	Biopsy-verified coeliac disease or seropositivity for coeliac disease autoantibodies	Heart disease (MI or AP) from national hospitalisation or death register	Coeliac disease: 28,190 Controls: 219,932 **Heart disease**: Coeliac disease: 991 Controls: 8254 **MI**: Coeliac disease: 658 Controls: 5926 **AP**: Coeliac disease: 498 Controls: 3769	**Median (range) age**: Coeliac disease: 29 (0–95) **Women**: Coeliac disease: 62.6% Seropositive:62.5%	**HR (95% CI)**: Heart disease: 1.19 (1.11, 1.28) MI: 1.11 (1.01, 1.21) AP: 1.27 (1.15, 1.40)	Controls were matched for age, sex, county and calendar year. Models were stratified for age, sex, county and calendar period. Controls included some individuals with unrecognised coeliac disease: their follow-up ended at their date of coeliac disease diagnosis. No details of gluten-free diet provided. This study is also listed in Table 2.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Ludvigsson, 2012 [26] Prospective case–control	Biopsy-verified coeliac disease from a pathology register	Stroke (including cerebral haemorrhage and cerebral infarction) from national hospitalisation register	Coeliac disease: 28,676 Controls: 141,806 **Stroke**: Coeliac disease: 785 Controls: 2937	**Median (range) age**: Coeliac disease: 30 (0–95) Controls: 29 (0–95) **Women**: Coeliac disease: 62.1% Controls: 62.3%	**HR (95% CI**: Stroke: 1.13 (1.03, 1.24) Ischaemic stroke: 1.10 (1.00, 1.21) Brain haemorrhage: 1.13 (0.93, 1.379 Stroke (additionally adjusted): 1.11 (0.96, 1.29)	Controls were matched for age, sex, county and calendar period. Analyses were adjusted for level of education. Additionally adjusted models were also adjusted for type 1 diabetes, rheumatoid arthritis and antihypertensive medication and lipid-lowering medication. Comparison group included some individuals with unrecognised coeliac disease: their follow-up ended at their date of coeliac disease diagnosis.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

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Table 1 (*continued*)

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participant age and sex	Main findings	Comments	Risk of bias
Hervonen, 2012 [20] Case–control	Diagnosis of dermatitis herpetiformis from local hospital records	IHD or cerebrovascular death from national death register	Dermatitis herpetiformis: 476 Ischaemic heart disease death: 25 Cerebrovascular disease death: 4 Circulatory system disease death: 35	**Mean (range) age**: 42.8 (3–84) **Women**: 50%	**SMR (95% CI)**: Ischaemic heart disease: 0.86 (0.15, 1.26) Cerebrovascular disease: 0.38 (0.10, 0.97) Circulatory system disease: 0.73 (0.51, 1.01)	No details of gluten-free diet provided. Standardised for age, sex and calendar period. Individuals with dermatitis herpetiformis had been on gluten-free diet. Partially the same data as Viljamaa and colleagues, 2006.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

Abbreviations: SD: standard deviation; OR: odds ratio; HR: hazard ratio; CI: confidence interval; SMR: standardised mortality ratio; MI: myocardial infarction; AP: angina pectoris; CVD: cardiovascular disease; IHD: ischaemic heart disease; tTGA: tissue transglutaminase antibody; EMA: endomysial antibody; GDF: gluten-free diet; HRT: hormone replacement therapy; NSAIDs: non-steroidal anti-inflammatory drugs.

were included in the meta-analyses. Three sets of analyses from the same group of investigators also included the same participants, although the exact extent of the overlap was not clear [24–26]. However, as these analyses had different outcomes (incident CHD, death from CHD and incident stroke), we treated them as separate investigations.

Coeliac disease and CHD

Associations between coeliac disease or dermatitis herpetiformis and CHD were examined in 12 sets of analyses from eight studies [20,23,24,27,29,30,32,35] and are shown in Fig. 1. For CHD, the pooled HR for incident disease was 1.05 (95% confidence interval (CI): 0.93, 1.19) and the overall SMR was 1.21 (0.99, 1.49). Regardless of the outcome, the study-specific association estimates varied in direction and there was substantial heterogeneity (I^2: 69.2%). Point estimates from the two studies of dermatitis herpetiformis suggested a decreased risk [20,30], and excluding these accentuated the overall estimate to 1.15 (95% CI: 1.04, 1.28), although this observation did not markedly differ from the result including these studies ($p = 0.1$).

Coeliac disease and stroke

The association between coeliac disease and incident cerebral infarction or haemorrhage was also examined in 12 sets of analyses from eight studies [20,23,26,27,29,30,32,35] (Fig. 2). In studies with incident cerebrovascular disease as the outcome and an internal comparison group, the overall HR for stroke or brain haemorrhage was 1.10 (95% CI: 1.00, 1.21). The pooled SMR for cerebrovascular disease death was 1.43 (95% CI: 0.97, 2.10) in studies comparing individuals with coeliac disease or dermatitis herpetiformis with a standard population. There was moderate heterogeneity among the estimates (I^2: 32.6%). When analysed separately, the pooled estimates were similar for brain haemorrhage (HR: 1.16, 95% CI: 0.97, 1.37) and stroke (HR: 1.09, 95% CI: 0.93, 1.27; $p = 0.9$) (Appendix 2, Fig. S2).

Coeliac disease and circulatory system disease

We identified nine sets of analyses of the associations between diagnosed coeliac disease or dermatitis herpetiformis and death from circulatory system disease (ICD-10 codes I00–I99 and/or ICD-9 codes 390–459) in eight studies [17,19,20,25,27,30,31,35] (Fig. S3, Appendix 2). We made a post hoc decision to analyse these outcomes separately as they included ischaemic disease as well as circulatory system diseases with other aetiologies. The study-specific estimates were considerably heterogeneous (I^2: 80.7%), varying from a 0.42- to 2.50-fold risk of death from circulatory system disease. Taken together, these provided no clear evidence for coeliac disease or dermatitis herpetiformis being related to circulatory disease mortality (random-effects estimate: 1.10, 95% CI: 0.89,

Table 2 Summary of studies of unrecognised coeliac disease and ischaemic cardiovascular disease.

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participants age and sex	Main findings	Control for confounding and other comments	Risk of bias
West, 2003 [33] Cross-sectional	Seropositivity for EMA antibodies with no self-reported coeliac disease	Self-reported stroke or heart attack/AP	EMA positive: 87 EMA negative: 7265 **EMA positive**: Stroke: 2 Heart attack/AP: 2 **EMA negative**: Stroke: 109 Heart attack/AP: 487	**Mean (SD) age**: 59 (8.9) **Women**: EMA positive: 65.5% EMA negative: 59.0%	**OR (95% CI)**: Stroke: 1.54 (0.37, 6.35) Heart attack/AP: 0.33 (0.08, 1.34)	Estimates were unadjusted. Coeliac disease cases had not been on gluten-free diet.	Confounding: critical risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: serious risk Overall bias: critical risk
Lohi, 2009 [22] Cohort	Seropositivity for coeliac disease autoantibodies	Death of ischaemic heart disease or stroke from national death register	tTGA negative: 6783 tTGA positive: 204 EMA negative: 6913 EMA positive: 74 **Death from ischaemic heart disease**: tTGA positive: 30 tTGA negative: 904 EMA positive: 4 EMA negative: 930 **Death from stroke**: tTGA positive: 24 tTGA negative: 334 EMA positive: 4 EMA negative: 354 **Death from circulatory disease**: tTGA positive: 69 tTGA negative: 1482 EMA positive: 12 EMA negative: 1539	**Mean (SD) age**: tTGA negative: 50.8 (14.0) tTGA positive: 59.1 (14.2) EMA negative: 51.1 (14.1) EMA positive: 49.2 (11.8) **Women**: tTGA negative: 53.7% tTGA positive: 61.3% EMA negative: 53.7% EMA positive: 72%	**HR (95% CI)**: **Death from ischaemic heart disease**: *tTGA positive*: 0.90 (0.62, 1.30) *EMA positive*: 0.49 (0.19, 1.30) **Death from stroke**: *tTGA positive*: 1.82 (1.20, 2.76) *EMA positive*: 1.20 (0.45, 3.23) **Death from circulatory system disease**: *tTGA positive*: 1.23 (0.97, 1.57) *EMA positive*: 0.85 (0.48, 1.50)	Adjusted for age and sex. Coeliac disease cases had not been on gluten-free diet.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Anderson, 2007 [15] Prospective case–control	EMA positivity from regional immunology laboratory records	Death from circulatory disease from regional death register	EMA positive: 490 Death from circulatory disease among the EMA positive: 9	**Mean (range) age**: EMA positive: 45 (0–88) **Women**: not reported.	**SMR (95% CI)**: Death from circulatory disease: 0.74 (0.26, 1.23)	Standardised for age and sex. No details of gluten-free diet provided.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

(*continued on next page*)

Table 2 (*continued*)

Author, year Design	Exposure ascertainment	Outcome ascertainment	*N* exposure *N* outcome	Participants age and sex	Main findings	Control for confounding and other comments	Risk of bias
Ludvigsson, 2009 [25] Prospective case–control	Biopsy-verified coeliac disease or seropositivity for coeliac disease autoantibodies	Cardiovascular death from national death register.	Seropositive: 3719 Controls: 228,632 **Cardiovascular death**: Seropositive: 45 Controls: 9295	**Median (range) age**: Seropositive: 36 (0–91) Controls: not reported **Women**: Seropositive: 62.1% Controls: not reported (sex-matched)	**HR (95% CI)**: **Cardiovascular death**: Seropositive: 1.27 (0.91, 1.76)	Controls were matched for age, sex, county and calendar year. Models were stratified for age, sex, county and calendar period. Control group included some individuals with unrecognised coeliac disease: their follow-up ended at their date of coeliac disease diagnosis. No details of gluten-free diet provided. This study is also described in Table 1.	Confounding: moderate risk. Selection of participants: low risk Measurement of exposure low risk: Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Rubio-Tabia, 2009 [28] Cross-sectional analyses in a cohort study	Seropositivity for coeliac disease autoantibodies	Cardiovascular death from national death register	tTGA and EMA positive: 11 tTGA negative: 8833 **Cardiovascular death**: tTGA and EMA positive: 1 tTGA negative: 736	**Age range**: <25–40+ **Women**: 1%	**OR (95% CI)**: Death from cardiovascular disease: 1.09 (0.17, 7.01)	Analyses shown here were unadjusted. Coeliac disease cases had not been on gluten-free diet.	Confounding: critical risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: critical risk Measurement of outcomes: moderate risk Overall bias: critical risk
Godfrey, 2010 [18] Case–control	Seropositivity for coeliac disease autoantibodies	IHD or cerebrovascular disease from local hospitalisation register	tTGA and EMA positive: 127 tTGA negative: 254 Outcome: Not reported.	**Median (range) age**: tTGA and EMA positive:63 (52–88) tTGA negative: 63 (52–88) **Women**: tTGAb and EMA positive: 51% Controls: 52%	**OR (95% CI)**: IHD: 1.03 (0.58, 1.83) Cerebrovascular disease: 0.99 (0.45, 2.21)	Controls matched for age and sex. No details of gluten-free diet provided.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: low risk Missing data: Measurement of outcomes: moderate risk Overall bias: serious risk
Canavan, 2011 [16] Cohort	Seropositivity for EMA with no self-reported coeliac disease	Death register record of death due to circulatory disease	EMA positive: 87 EMA negative: 7440 Outcome: Not reported.	**N (%) by age group**: EMA positive: <55 years: 37 (42.5) 55–64 years: (30 (34.5)	**HR (95% CI)**: Death from circulatory system disease: 1.39 (0.66, 2.92)	Adjusted for age, sex, socio-economic position and smoking. Coeliac disease had not been on gluten-	Confounding: serious risk. Selection of participants: low risk Measurement of

				≥65 years: 20 (23.0) EMA negative: <55 years: 2794 (37.6) 55–64 years: 2280 (30.6) ≥65 years: 2366 (31.8) **Women**: EMA positive: 65.5% EMA negative: 59.0%		free diet. This study used the same data as West and colleagues (2003) but had a different design and different outcome.	exposure: low risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk
Ludvigsson, 2011 [24] Prospective case–control	Seropositivity for coeliac disease autoantibodies (EMA, tTGA or anti-gliadin)	Heart disease (MI or AP) from national hospitalisation register	Seropositive: 3658 Controls: 219,932 **Heart disease**: Seropositive: 62 Controls: 8254 **MI**: Seropositive: 37 Controls: 5926 **AP**: Seropositive: 34 Controls: 3769	**Median (range) age**: Seropositive: 35 (0–91) **Women**: Seropositive: 62.5%	**HR (95% CI)**: Heart disease (MI or AP): 1.14 (0.87, 1.50) MI: 0.97 (0.68, 1.37) AP: 1.36 (0.94, 1.97)	Controls were matched for age, sex, county and calendar year. Models were stratified for age, sex, county and calendar period. Seropositivity for anti-gliadin antibodies used to define coeliac disease cases. Controls included individuals who were subsequently diagnosed with coeliac disease: their follow-up ended at their date of diagnosis. No details of gluten-free diet provided. This study is also described in Table 1.	Confounding: serious risk. Selection of participants: low risk Measurement of exposure: moderate risk Missing data: low risk Measurement of outcomes: moderate risk Overall bias: serious risk

Abbreviations: SD: standard deviation; OR: odds ratio; HR: hazard ratio; CI: confidence interval; SMR: standardised mortality ratio; MI: myocardial infarction; AP: angina pectoris; CVD: cardiovascular disease; IHD: ischaemic heart disease; tTGA: tissue transglutaminase antibody; EMA: endomysial antibody; GDF: gluten-free diet; HRT: hormone replacement therapy; NSAIDs: non-steroidal anti-inflammatory drugs.

1.36). Both studies of dermatitis herpetiformis showed protective associations [20,30].

Unrecognised coeliac disease and CHD or cerebrovascular disease

We identified eight investigations of unrecognised coeliac disease, defined as seropositivity for coeliac disease-specific tissue tTg antibodies or endomysial antibodies and no record of a histological diagnosis of coeliac disease [15,16,18,22,24,25,28,33] (Table 2). All study-specific prevalence estimates indicated that CHD and stroke or death from these diseases were equally common among seropositive individuals and the comparison group [18,28,33]. Similarly, no association between unrecognised coeliac disease and death from CHD or cerebrovascular disease was reported in prospective analyses [15,16,22,25], although the estimates from one study suggested that seropositivity might be related to an increased risk of death from stroke [22]. No association was reported in the only prospective investigation of the relationship between unrecognised coeliac disease and CHD (HR for myocardial infarction or angina pectoris: 1.14, 95% CI: 0.87, 1.50) [24]. However, all the study-specific estimates were based on small numbers of CHD or cerebrovascular disease events among the seropositive individuals.

Small study effects

A funnel plot of the main findings against their standard errors from each study included in our meta-analyses indicated that a mix of positive, negative and null associations was reported (Appendix 2, Fig. S4). There was little evidence for an association between study power and findings (Appendix 2, Fig. S4; p: 0.2) but as tests for funnel plot asymmetry tend to have low power [38], we cannot exclude the possibility that the studies we analysed represent a body of research selected for publication due to point estimates, though not always the confidence intervals, indicating higher risks among participants with coeliac disease.

Potential sources for heterogeneity

We examined adjustment for confounding, characteristics of the comparison group, gluten-free diet and specific (e.g., myocardial infarction) versus non-specific (e.g., circulatory system disease) outcome as potential sources of heterogeneity. We found no clear evidence of the study-specific findings varying by these characteristics (all p-values >0.1), although studies with adjustment for confounding were slightly less likely to report an association ($p = 0.036$) (Appendix 2, Table S1). The results from the random-effects models based on the Knapp–Hartung variance estimator were compatible with those based on the DerSimonian and Laird method, although their confidence intervals were wider (Appendix 2, Fig. S6).

Risk of bias

All studies of clinically diagnosed coeliac disease had a prospective design (Table 1), whereas the studies of unrecognised coeliac disease also included cross-sectional and case–control studies (Table 2). Exposure and outcome measurements had low or moderate risk of bias as coeliac disease and dermatitis herpetiformis diagnoses were ascertained from clinical records in all studies bar one, which also included self-reported cases of coeliac disease [29] (Table 1). Unrecognised coeliac disease was ascertained from serological tests in all studies (Table 2), although in one study the exposed group included individuals seropositive for gliadin antibodies [24], which are not specific to coeliac disease [42–44]. Outcomes were ascertained from national hospitalisation or death registers in all studies except one, in which they were self-reported [33]. The findings from the studies with self-reported exposure [29] or outcome [33] were similar to those of other studies. Participant selection is unlikely to have introduced notable bias, as cases were compared with disease-free participants from the same population [16,18,23–26,28,31–33] or with a standard population [15,17,19,20,27,29,30,35].

Age, sex, gluten-free diet, adiposity and dietary factors are among the potential confounders to the associations of coeliac disease or dermatitis herpetiformis with atherosclerotic disease. The majority of studies included adjustment for at least age and sex, either as the only covariates [15,18,19,22] or in addition to some combination of calendar year, geographical area and follow-up time [17,20,23–27,29,30,35,45]. One study also included additional adjustment for socio-economic position and smoking [16] and another for co-morbidities, medications and gluten-free diet [31]. Two sets of estimates were unadjusted [28,33] (Tables 1 and 2).

Discussion

Summary of main findings

For CHD, the pooled HR for incident disease was 1.05 (95% CI: 0.93, 1.19) and the overall SMR 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.

We found no clear evidence of unrecognised coeliac disease (seropositivity for coeliac disease-specific autoantibodies) being related to the prevalence or incidence of CHD or cerebrovascular disease [15,16,18,22,24,28,33]. However, all the study-specific estimates were based on relatively small numbers of outcomes and were thus likely underpowered. Furthermore, in the largest prospective investigation of unrecognised coeliac disease and CHD, the unrecognised group included individuals who were seropositive for gliadin antibodies [24]. As antibodies against gliadin (the gluten component in wheat) are not specific to coeliac disease (elevated concentrations can be detected in healthy people and in those with other autoimmune

diseases) [42–44], this may have led to exposure misclassification and diluted the association estimates in this study.

Potential biological mechanisms

The biological mechanisms for the role of coeliac disease in CHD and cerebrovascular disease pathology are not fully understood, but several possible pathways have been suggested. Individuals with coeliac disease suffer from chronic low-level inflammation, which can drive atherosclerosis and vascular damage [46]. Findings from a meta-analysis of two other inflammation-related bowel diseases, Crohn's disease and ulcerative colitis, suggesting that these are associated with a modest increase in cardiovascular disease risk, support this possibility [47]. However, there is also evidence that the autoimmune reaction in coeliac disease, marked by autoantibodies against tTG (an enzyme involved in the ingestion of gluten), has anti-angiogenic effects [7,48,49], which may alter the normal functioning of the vascular system. Furthermore, coeliac disease, particularly when untreated or when the adherence to a gluten-free diet is poor, could lead to malabsorption of nutrients and thus low circulating concentrations of folate or elevated concentrations of homocysteine [50], which are implicated in the pathology of cardiovascular disease [51,52].

Heterogeneity and risk of bias

Our systematic review was based on comprehensive searches of four electronic databases, and the searches were not limited to any study design or language of publication. As we focussed on published literature, it is possible that if a large amount of unpublished null results exists in this area, then our meta-analyses have overestimated the true association. We found no clear evidence for small-study effects but as the tests for these generally have low power, it is possible that some, for example due to publication bias, have influenced our findings. The moderate to considerable heterogeneity in the study-specific association estimates limits the interpretability of our meta-analysis, particularly as none of the potential sources for heterogeneity we examined clearly explained this variation.

As all the studies of clinically diagnosed coeliac disease or dermatitis herpetiformis had a prospective design, it unlikely that our pooled estimates have been influenced by reverse causality. In all bar two studies [29,33] coeliac disease or dermatitis herpetiformis exposures were based on clinical diagnoses or laboratory tests and cardiovascular disease outcomes from local or national registers, which are generally not prone to recall bias. However, the possibility of exposure misclassification or measurement error cannot be excluded. Validation studies suggest that although health-care and death registers in the countries where the studies we reviewed were conducted (Finland, Italy, Sweden, the UK and the United States) contain reasonably accurate diagnostic information, they miss a proportion of cardiovascular disease events [53–57]. Using data from more than one register would help capture a larger proportion of the incident cases of atherosclerotic disease, but a combination of two registers (hospitalisation and mortality) has been used in only two studies [24,31]. Such under-ascertainment of the outcome may have diluted the study-specific association estimates and led to an underestimate of the average association in our meta-analyses.

It is unlikely that the choice of comparison group has significantly biased our meta-analyses, as the study-specific results were based on comparisons of individuals with coeliac disease or dermatitis herpetiformis with disease-free participants from the same population [16,18,23–26,28,31–33] or to a standard population [15,17,19,20,27,29,30,35]. Previous studies with an internal comparison group have shown larger estimates for mortality risk than studies using national population mortality data as the comparison [58], but we observed no such difference in our meta-analyses. If anything, the meta-regression point estimates suggest that the reported associations are slightly larger in studies in which SMRs, rather than internal comparisons, were presented. However, lack of control for potentially relevant covariates, particularly gluten-free diet and other dietary factors, was a limitation in the majority of the studies. Thus, residual confounding from unknown or unmeasured confounders may have led to under- or overestimates in the study-specific associations and, consequently, in our meta-analysis estimates.

Directions for further research

CHD, stroke and cerebral haemorrhages are major causes of morbidity and mortality worldwide, incurring considerable cost to individuals as well as health-care systems [59,60]. The burden of atherosclerotic disease could be reduced by better targeting primary prevention strategies to individuals and groups who are at particular risk. One such risk group could be individuals with coeliac disease. Our meta-analyses lend some support to the notion that coeliac disease and dermatitis herpetiformis are associated with the risk of some, although not all, cardiovascular outcomes. However, many study-specific estimates were based on small numbers, and they may have been influenced by residual confounding and other sources of bias. Adequately powered prospective studies of histologically diagnosed and unrecognised coeliac disease, with appropriate adjustment for potential confounders, would help confirm or refute these findings. The role of a gluten-free diet in the relationship between coeliac disease and cardiovascular diseases would also merit further research.

Conclusions

Our meta-analyses lend some support to the notion that coeliac disease and dermatitis herpetiformis are associated with the risk of CHD and cerebrovascular disease. However, many study-specific estimates were based on a small number of outcomes, and they may have been influenced by residual confounding and other sources of bias. Our

systematic review highlighted a need for adequately powered prospective studies with appropriate adjustment for potentially confounding factors in this area.

Author contributions

KH and KK conceived the study. KH, OAK and AA systematically searched electronic databases, identified relevant studies and extracted data from these. KAOT assisted in developing the search strategy, conducting the searches and extracting data. KH planned and conducted the statistical analyses. KH wrote the first draft of the paper. KH, OAK, KAOT, MM and KK participated in critically reviewing and revising the manuscript. The funding bodies had no role in the design or conduct of the study, analysis or interpretation of the data, manuscript preparation or decision to submit the manuscript for publication.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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Abbreviations

RR	risk ratio
OR	odds ratio
HR	hazard ratio
IRR	incidence rate ratio,
CI	confidence interval
SD	standard deviation,
GFD	gluten-free diet
BMI	body mass index
tTGA	tissue transglutaminase antibody

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2015.05.004.

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