First-degree relatives

Bibliographic reference	**Almeida et al. (2008)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Brazil
Number of patients	N=72 patients with CD (modified ESPGHAN criteria) N=188 first-degree relatives
Study population	First-degre relatives of CD patients attending the Brasilia University Hospital Pediatric Gastroenterology out-patient clinic or the Celiac

	Disease Investigation Centre in Brasilia between March 2001 and November 2004 Of 307 relatives, 188 agreed to screening. 60% (113) were female mean 29.9 years (range 1 to 75, SD 16.8) 102 parents (42 fathers, 60 mothers, aged 25 to 75, median age 36 years) 76 siblings (31 brothers and 45 sisters, 1 to 75 years, median age 11.5 years) 10 offspring (2 males, and 8 females, aged 1-45 years, median age 9.65 years)
Control	none
Details of coeliac testing	Index patients were diagnosed following the modified ESPGHAN criteria All were on a gluten-free diet during serological testing – IgA-EMA was used as first-level; all positive sera were then tested for IgA-tTG using ELISA method (Quanta Lite Human tTG IgA – INOVA Diagnostic Inc, San Diego, CA, USA); duodenal or small intestinal biopsy was performed in all those positive in this test Diagnosis of CD was given to those with positive serological tests and a grade I to III small intestinal lesion.
Length of follow-up	n/a
Results	**Postive IgA-EMA, high levels of IgA-tTG and histological changes characteristic of CD were found in 9 patients (4.8%) of 188 tested.** Of the 9 patients: - 5 sisters, 1 brother and 3 mothers - 1 Marsh I (described in study as ilfiltrative) and 8 March III (described in study as flat destructive) - Age 2 to 75 years, median 25 years Presenting clinical features ranged from - no clinical symptoms (n=1) - gastrointestinal symptoms (n=6); 2 also had other symptoms: 1 had decreased appetite, apathy and mouth ulcers, and another had irritability, apathy and painful joints. - other symptoms only (n=2, 1 patient had patinful joints & osteoporosis and another had irritability, apathy, muscle and joint pain, anemia, and osteoporosis).
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	none

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Ascher et al. (1997)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Sweden
Number of patients	N=97 patients with coeliac disease (96 families) N=164 siblings
Study population	Patients with coeliac disease were diagnosed between 1970 and 1991 at the department of paediatrics, East University Hospital, Göteborg where the patient was diagnosed according to the original ESPGHAN criteria)
Control	None
Length of follow-up	n/a
Details of coeliac testing	Index patients were diagnosed with original ESPGHAN criteria For siblings, HLA typing where those carrying HLADR3-DQ2 or DR5/7-DQ2 (or those who shared other HLA risk haplotypes with their sibling that had coeliac) had small intestinal biopsy
Results	Of 85 siblings with HLA typing DR3-DQ2 or DR5/7-DQ2, 2 dropped out and one had already had a small biopsy sample showing normal mucosa. **Of the remaining 82 siblings, 4.9% (8/164) were found with intestinal mucosa compatible with coeliac disease; including the patient with a previous diagnosis, the rate of CD was 5.5% (9/165)** Of the 73 which were determined not to have coeliac disease, 9 with various degrees of mucosal inflammation but normal villous height

	and crypt depth became normal histologically despite gluten intake. Four additional patients had slight histological changes but were excluded from further analysis because the final diagnosis was not clear.
Source of funding	Grants from Wilhelm and Martina Lundgren Foundation, the Göteborg Medical Society, the First of May Flower Annual Campaign for Children's Health, 'Förenade Liv' Mutual Group Life Insurance Company, 'Samariten' foundation, the Swedish Coeliac Disease Association, the Royal Society of Arts and Sciences in Göthenburg, Sweden and the Swedish Society for Medical Research.
Conflicts of interest	Not reported
Comments	

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Biagi et al. (2008)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Italy
Number of patients	N=73 index patients N=158 first-degree relatives
Study population	Inclusion: adult first degree relatives of 73 coeliac patients referred to an out-patient clinic, diagnosed by duodenal biopsy and coeliac antibodies, between Jan 1999 – June 2006
Control	none

Length of follow-up	N/A (participants were followed up for 1year and re-contacted by phone but these results were not presented here as patients may have been receiving treatment / on a GFD in this time period)
Details of coeliac testing	Index patients were biopsy-confirmed. For family members: IgA-EMA (indirect immunofluorescence kit, The Binding Site, Birmingham, UK using monkey oesophagus sections and goat antihuman IgA antibodies) Those +ve were biopsied. Duodenal biopsy confirmed the diagnosis of coeliac disease in all those who were +ve
Results	**Initial prevalence, N=28/158 (17.7%, 95% CI 12.1 to 24.6)** Mean age: 46.4yrs±16.9 20 females
Source of funding	Not reported
Conflicts of interest	Authors report that none were declared
Comments	

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**da Silva Kotze et al. (2013)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Brazil
Number of patients	N= 3 sets of twins (2 monozygotic twins with biopsy-confirmed CD and 1 set of dizygotic twins where the male but not the female had CD)

	N=9 first-degree relatives
Study population	First-degree relatives of 3 sets of twins, including: Family A (monozygotic) – mother (25 years) and father (34 years) Family B (monozygotic) – mother (44 years), father (53 years), sister (24 years), brother (11 years) Family C (dizygotic) – mother (42 years), 2 brothers (21 and 18 years)
Control	none
Length of follow-up	n/a
Details of coeliac testing	Index patients were confirmed as coeliac bybiopsy. For family members: IgA EMA test and, if positive, gastrointestinal endoscopy with duodenal biopsy. CD considered if endoscopy changes in duodenum mucosa with IEL count > 40% and a response to a GFD
Results	Positive IgA-EMA and biopsy in: - Father of pair/family A (1/2) - None of the pair/family B (0/4) - Two members (including the mother) of pair/family C (2/3) **Overall prevalence: 33% (3/9)**
Source of funding	Authors report there are no conflicts of interests related to funding.
Conflicts of interest	Authors report no conflicts of interests related to disclosures were declared
Comments	

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Esteve et al. (2006)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES

	5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Spain
Number of patients	N=82 patients with CD N=221 first-degree relatives
Study population	Inclusion: first degree relatives of patients with CD and DQ2+ recruited consecutively in an outpatient clinic at one of 3 hospitals between January 2004 and June 2005 Exclusion of relatives: living in a distant place, being < 18 months old, refusal to participate Index: 32 males, 50 females, mean 16.5 years (12 months to 77 years) Relatives: 276 were identified and 221 were included (104 males, 117 females, mean age 34 years [22 months-72 years])
Control	None
Length of follow-up	n/a
Details of coeliac testing	Index patients were confirmed as coeliac with ESPGHAN criteria Family members: HLA-DQ2 genotyping EMA (indirect immunofluorescence assay at 1:5 dilution, BioMedical Diagnostics, Marne-la-Vallée, France with monkey distal oesophagus as substrate) IgA tTGA (ELISA, Celikey, Sweden Diagnostics GmbH, Frieburg, Germany using recombinant human tissue transglutaminase; values > 8 U/mlo were considered positive) Total serum IgA with rate nephelometry (BN II, Dade Behring, Frankfurt, Germany; IgG-class EMA was determined if IgA deficient) Biopsy for all patients (regardless of serology results)
Results	58.8% (130/221) were DQ2+ 14.5% (20) of those who had DQ2+ but negative serology refused biopsy Of 110 with biopsy, the results showed: 29.2% (64) Marsh 0 (30.0% overall) 24.6% (32) Marsh I (14.5% overall) 0.8% (1) Marsh II (0.45% overall)

	10% (13) Marsh III (5.9% overall) Overall, histological abnormalities were found in 46 (20.8%)
Source of funding	Fundació Banc de Sabadell
Conflicts of interest	Paper reports none were declared
Comments	

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Oliveira et al. (2013)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Portugal
Number of patients	N=163 children with CD N=268 (232 parents, 36 siblings)
Study population	Inclusion: first-degree relatives of CD patients attending a Paediatric Gastroenterology outpatient clinic at a University Hospital between January 2009 and July 2010 Exclusion: those having a GFD and a prior diagnosis of CD 232 parents: 143 mothers, 89 fathers; median age 38 years (range 22-64) 36 siblings: 11 sisters, 25 brothers; median age10 years (range 12 months to 28 years)

	50.3% (82) of children had more than one relative that participated in the study (2 per child in 61 cases, 3 per child in 19 cases, and 4 per child in 2 cases)
Control	None
Length of follow-up	n/a
Details of coeliac testing	Index patients were diagnosed according to ESGHAN criteria for CD Family members: capillary immunoichromatographic rapid test (BIOCARD™ coeliac test) qualitatively detecting IgA and IgA-tTG from aipllary blood (10 microliters) If this test was positive, subjects had IgA tTG by ELISA from venous blood and duodenal biopsy (>10 U/mL was considered positive) IgG human recombinant antitransglutaminase antibody was used if IgA deficiency was detected. CD was diagnosed if IgA tTG was positive and biopsy revealed Marsh type 3 lesions.
Results	Initial screening with BIOCARD™: positive in 4.5% (12) of first degree relatives (9 mothers, 2 fathers, 1 brother) 1.1% of tests were suggestive of IgA deficiency Serological testing and small bowel histology: All but one patient (n=11) who was positive on initial screening had further testing with IgA tTG and duodenal biopsy **CD was diagnosed in 2.6% (7/268) first-degree relatives** - 5 mothers, 2 fathers – mean 39 years old (range 27-56); majority had mild symptoms, high titre of IgA-tTG and histopathological findings on biopsy
Source of funding	Not reported
Conflicts of interest	Study reports that authors had none
Comments	

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Rubio-Tapia et al. (2008)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html)

	1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	USA
Number of patients	N=113 CD 'index' patients (26% [30/113] were related to each other and 2 had no first-degree family members) N=574 first-degree relatives were initially contacted by letter N=344 (60%) included (162 were non-responders, 21 did not participate, 45 were previously screened, and 2 had self-diagnosed so were not included) Not all first-degree relatives were biopsied, even if they had positive serology (66 of 344 were biopsied) - results were presented separately for those with and without biopsy
Study population	First degree relatives of patients with CD (diagnosed with biopsy) from southeast Minnesota which were identified from the Rochester Epidemiology Project which links medical records of Olmsted Country residents; all patients with CD were seen at 1 or 2 centres which provide all heatlhare in the region Exclusion: previously tested relatives Index patients: mean age 42 years (range 1.1-81.6), 79% (70/113) female, 64% (72) had HLA available (60 DQ2+, 11 DQ2/DQ8+ and 1 DQ8+) First-degree relatives: mean age 42.4 years (only 9 were < 5 years), 60% (200) female, 22% (75) were partents, 38% (132) were children and 40% (137) were siblings
Control	none
Length of follow-up	n/a
Details of coeliac testing	Index patients were confirmed as coeliac by biopsy and response to GFD Family members: Subjects were biopsied if there were any positive autoantibody (tTGA human antigen INOVA Diagnostics Inc, San Diego, CA: ≥ 20 U/mL and EMA with indirect immunofluroescensce on monkey oesophagus – BINDAZYME, The Binding Site Ltg, Birmingham, UK: ≥ 1:5) or seronegative family members with gastrointestinal symptoms and HLA-DQ at risk for CD CD diagnosis on the basis of Marsh/Oberhuber stages 2&3

Results	Of all 574 first-degree relatives were approached (by mail), 162 did nto respond and 21 chose not to participate; 45 were then excluded because they had previously been screened and 2 had already self-diagnosed so were excluded) Of 344 included, serology and biopsy results in first-degree relatives were as follows: (biopsy was tested in 66 of 344 relative – 79% [37/47] of those with positive tTGA and 85% [28/33] of those with positive EMA)

Serological status	# of relatives	Intestinal biopsy				
		Normal (Marsh0)	Marsh 1	Marsh 2	Marsh 3	Not done
IgA EMA+, tTGA+	33	0 (0%)	1 (3%)	1 (3%)	26 (79%)	5 (15%)
IgA EMA-, tTGA+	14	4 (29%)	2 (14%)	0 (0%)	3 (21%)	5 (36%)
IgA EMA-, tTGA-	297	26 (9%)	0 (0%)	0 (0%)	3 (1%)	268 (90%)
Total	344	30 (9%)	3 (1%)	1 (3%)	32 (9%)	278 (81%)

	Definite CD was diagnosed in 39 of 344 first degree relatives (11%) with either serology and/or biopsy: 16 (49%) siblings, 11 (33%) children, 6 (18%) parents. Of these 39 cases, 21 were males, classic symptoms were in 13% (2 siblings, 2 parents, 1 child), atypical in 33% (8 siblings, 3 parents, 2 children) and silent in 54% (11 siblings, 2 parents, 8 children) [atypical manifestations included constipation and bloating in 7, severe fatigue with nonspecific musculoskeletal pain in 4, iron deficiency anaemia in 2] 3 of the 39 (8%) had autoimmune diseases: Graves' disease, Hashimoto's thyroiditis and type I diabetes.
Source of funding	American College of Gastroenterolgoy International training Grant in Gastrointestingal Allergy and Immunology Research, CTSA grant from the National centre for Research Resources and NIH grants
Conflicts of interest	Not reported
Comments	

Definitions of abbreviations are given at the end of this document.

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Bibliographic reference	**Szaflarska-Szczepanik et al. (2001)**
Study type	Cross-sectional survey
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? NO – Unclear is consecutive sample recruited

	3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = MODERATE
Country	Poland
Number of patients	N=127 (?) children with CD N=254 pairs of parents of children with CD
Study population	Inclusion: pairs of parents randomly selected children with celiac disease diagnosed in accordance with the ESPGHAN criteria 25-58yrs (mean 38.8yrs) 96.1% one child with coeliac disease N=5 (3.9%) two siblings with coeliac disease
Control	none
Details of coeliac testing	Index patients were diagnosed using ESPGHAN criteria Family members: Total IgA was measured, IgA/IgG EMA (indirect immunofluorescence) - those +ve were biopsied
Length of follow-up	n/a
Results	Total IgA normal in all **N=5 (2%) IgA EMA +ve** (3 were male) IgA EMA varied within the limits of +20 IF to +640 IF N=4/5 biopsied, all had atrophy of the villi of the mucous membrane in the small intestine, class IV (N=3) or class III/IV N=3 abdominal pains, N=3 short stature, N=1 no symptoms
Source of funding	Polish Scientific Research Commission
Conflicts of interest	Not reported

Comments

Definitions of abbreviations are given at the end of this document.

Bibliographic reference	**Vaquero, L. (2014)**
Study type	Cohort study
Study quality	The Joanna Briggs Institute Prevalence Critical Appraisal Tool (http://ijhpm.com/article_2870_607.html) 1. Was the sample representative of the target population? YES 2. Were study participants recruited in an appropriate way? YES (consecutive sample recruited) 3. Was the sample size adequate? YES 4. Were the study subjects and the setting described in detail? YES 5. Was the data analysis conducted with sufficient coverage of the identified sample? YES 6. Were objective, standard criteria used for the measurement of the condition? YES 7. Was the condition measured reliably? YES 8. Was there appropriate statistical analysis? YES 9. Are all important confounding factors/subgroups/differences identified and accounted for? YES 10. Were subpopulations identified using objective criteria? NA Overall risk of bias = LOW
Patient characteristics	Adult FDR's of CD cases diagnosed at University hospital of Leon were consecutively screened and invited to participate in the study. The diagnosis of CD in the index cases was made according to ESPGHAN criteria. 92 FDR's were HLA positive and of these, 67 agreed to undergo biopsy N= 67 Mean age = 34 years 33 females / 34 males
Co-morbid condition	First degree relatives
Investigations	All FDR's underwent : • HLA testing for DQ2 and DQ8 • IgA tTG testing • Upper endoscopy - histological samples graded according to MARSH criteria
Results	• Prevalence of positive serological marker was 25% (17/67) • Histopathological alterations found in 32/67 cases • 19/67 had Marsh 3 atrophy - positive diagnosis of CD =28.3% • 13/67 had Marsh stage 1 or 2 (19.4%)
Funding	Funded in part by a grant from Instituto de salud Carlos II, Co-funded by European regional development fund

Other comments	None