Appendix D: Evidence Tables

D.1 Review question 4.1

Adult studies

Bibliographic reference	Ludvigsson, J. F., Nordenskjold, A., Murray, J. A., and Olen, O. A large nationwide population-based case-control study of the association between intussusception and later celiac disease. BMC Gastroenterology 13, 89. 2013.
Study type	Case-control (where CD has been compared against non-CD in a group of patients with intussusception)
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? Yes, question clear 2. Cases and controls from comparable populations? Same population of Swedish male conscripts 3. Same exclusion criteria used for both cases and controls? Yes same exclusion criteria applied 4. What was participation rate for each group? Cases: controls: N/A; all blood tested, participation not required from either group 5. Participants and non-participants are compared to establish their similarities or differences? Yes; baseline characteristics the same between groups. 6. Cases are clearly defined and differentiated from controls: cases are defined in terms of seropositivity 7. It is clearly established that controls are not cases? Clear in the fact that cases are seronegative, but without biopy f all 144522 controls cannot be 100% certain that none have CD. For this study purposes, controls are clearly established as non-cases. 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? Yes, no person was to have had previous suspicion of CD or previous duodenal biopsy 9. Exposure status is measured in a standard, valid, and reliable way? Yes; serological testing for CD was standard 10. Main potential confounders are identified and taken into account in the design and analysis? Only single predictive factor considered other factors nottaken into consideration. As population all same age and gender from same country not likely to have highly differing baseline characteristics. 11. Have confidence intervals been provided? Yes
Aim	Examine the association between coeliac disease and previous intrassuception

<table>
<tr><td>Patient characteristics</td><td>Study Population: Patients with intrassuception, identified via a patient register with reference to international classification of disease codes.
Control Population: Each patient was matched with up to 5 controls for age, sex, calendar period and country of residence. Controls were identified via a government total population register. Controls must have had no previous duodenal/jejunal biopsy.
Number of patients in study population: 29096
Number of patients in control population: 144522
Number of patients excluded: Not specified
Median age: Study group: 30 (range 0-90) Control: Not specified, but age matched.
Males/females: Study group: 18005m/11091f Control group: 54978m/89544f
Country: Sweden
Other comments:</td></tr>
<tr><td>Source of funding</td><td>Government and charity</td></tr>
<tr><td>Sign/Symptom</td><td>Intrassusception</td></tr>
<tr><td>Reference standard</td><td>Small intestinal biopsy with villous atrophy (Marsh stage 3)</td></tr>
<tr><td>Results</td><td><table><tr><td></td><td>With Coeliac disease (n=29096)</td><td>Control (n=144522)</td></tr><tr><td>Previous intrassuception</td><td>34 (0.12%)</td><td>143 (0.10%)</td></tr></table>
Conditional Logistic regression:
Unadjusted OR for coeliac disease given previous intrasucception=1.17 (95%CI =0.84-2.05)

Further subgroup analysis was reported for:
Children diagnosed before the age of 2, Intrassuception requiring surgery or radiological intervention, Intrassuception requiring 2 or more healthcare contacts, males and females separately, data divided by age group, data divided by calendar period. No statistically significant effect was found for the predictive effect of intrasucception in any of these subgroups.</td></tr>
<tr><td>Comments</td><td>Care has been taken in this study to match case and control subjects on some baseline confounding factors. However, only a single predictive factor was considered, which means there is a high risk of confounding. It is unclear whether the assumptions for logistic regression were met, reducing confidence in the statistical analysis.</td></tr>
</table>

Bibliographic reference	Mollazadegan, K. and Ludvigsson, J. F. Coeliac disease does not affect visual acuity: a study of young men in the Swedish national conscripts register. 20100126. Scandinavian Journal of Gastroenterology 44(11), 1304-1309. 2009.
Study type	Case-control (people with and without coeliac disease were compared)
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? Yes, question clear 2. Cases and controls from comparable populations? Same population of Swedish male conscripts 3. Same exclusion criteria used for both cases and controls? Yes same exclusion criteria applied 4. What was participation rate for each group? Cases: controls: N/A; all blood tested, participation not required from either group 5. Participants and non-participants are compared to establish their similarities or differences? Yes; baseline characteristics the same between groups. 6. Cases are clearly defined and differentiated from controls: cases are defined in terms of seropositivity 7. It is clearly established that controls are not cases? Clear in the fact that cases are seronegative, but without biopsy of all controls cannot be 100% certain that none have CD. For this study purposes, controls are clearly established as non-cases. 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? Yes, no person was to have had previous suspicion of CD or previous duodenal biopsy 9. Exposure status is measured in a standard, valid, and reliable way? Yes; serological testing for CD was standard 10. Main potential confounders are identified and taken into account in the design and analysis? Only single predictive factor considered other factors not taken into consideration. As population all same age and gender from same country not likely to have highly differing baseline characteristics. 11. Have confidence intervals been provided? Yes
Aim	Examine the association between visual acuity and subsequent diagnosis of coeliac disease (also examined the association between visual acuity and coeliac disease that had already been diagnosed, but this element does not meet the inclusion criteria for this review).
Patient characteristics	**Study Population:** Men identified through the Swedish national inpatients register as having coeliac disease which led to an inpatient stay before or after conscription. In order to be eligible, visual acuity data had to be also available from the national conscripts register before 2000. Before 2000 most Swedish men were conscripted (80%-98% between 1996 and 2000). **Control Population:** Each patient was matched with up to 5 controls for age, sex, calendar period and country of residence.

<table>
<tr><td></td><td>Controls were identified via a government total population register.
Number of patients in study population: 69 with coeliac disease undiagnosed at the time of visual acuity testing (additional 996 with coeliac disease diagnosed before conscription – data not reported in this review)
Number of patients in control population: 6850
Number of patients excluded: study participants: 210 control participants: 543 (either were born outside of Sweden, coeliac diagnosis status or visual acuity data was not available).
Mean age: Study group: 18.9 (sd 0.5) Control group: 18.7 (sd 0.6)
Males/females: All male
Country: Sweden
Other comments: Only data for participants who were diagnosed with coeliac disease after the visual acuity data was gather are eligible for this review are reported below.</td></tr>
<tr><td>Source of funding</td><td>Government and charity</td></tr>
<tr><td>Sign/Symptom</td><td>Visual acuity</td></tr>
<tr><td>Reference standard</td><td>Inpatient stay related to coeliac disease as defined by international classification of disease codes (ICD-7: 286.00; ICD-8:269.00, 269.98, ICD-9: 579A; ICD-10: K90.0)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Coeliac disease (n=69)</td><td>Control (n=6850)</td></tr>
<tr><td>Impaired visual acuity (snellen fraction < 9)</td><td>25 (36.2%)</td><td>2418 (35.3%)</td></tr>
</table>
Adjusted logistic regression (adjusted for socioeconomic index, calander period, and presence/absence of diabetes mellitus): OR=1.04 (95% CI 0.9-1.19)
(No significant relation between visual acuity and coeliac disease)</td></tr>
<tr><td>Comments</td><td>Case and control participants were matched for baseline characteristics, which controls some confounding factors. However, only a single predictive factor was considered, which means there is a high risk of confounding. Participants were identified from a conscription register which may have biased the sample to less severe cases.</td></tr>
</table>

Bibliographic reference	Olen, O., Montgomery, S. M., Marcus, C., Ekbom, A., and Ludvigsson, J. F. Coeliac disease and body mass index: a study of two Swedish general population-based registers. 20100308. Scandinavian Journal of Gastroenterology 44(10), 1198-1206. 2009.
Aim	To examine the relation between body mass index (BMI) and in patient diagnosis of coeliac disease.
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? Yes, question clear 2. Cases and controls from comparable populations? Same population of Swedish male conscripts 3. Same exclusion criteria used for both cases and controls? Yes same exclusion criteria applied 4. What was participation rate for each group? Cases: controls: N/A; all blood tested, participation not required from either group 5. Participants and non-participants are compared to establish their similarities or differences? Yes; baseline characteristics the same between groups. 6. Cases are clearly defined and differentiated from controls: cases are defined in terms of seropositivity 7. It is clearly established that controls are not cases? Clear in the fact that cases are seronegative, but without biopsy of all controls cannot be 100% certain that none have CD. For this study purposes, controls are clearly established as non-cases. 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? Yes, no person was to have had previous suspicion of CD or previous duodenal biopsy 9. Exposure status is measured in a standard, valid, and reliable way? Yes; serological testing for CD was standard 10. Main potential confounders are identified and taken into account in the design and analysis? Only single predictive factor considered other factors not taken into consideration. As population all same age and gender from same country not likely to have highly differing baseline characteristics. 11. Have confidence intervals been provided? Yes
Study type	**PART 1** Cohort study **PART 2** Case-control study
Patient characteristics	**The study is split into two parts:** **PART 1** **Study Population:** Pregnant females identified from the Swedish medical birth register, aged 18-50, with data available on pre-pregnancy weight (restricted to women with weight 30-200 Kg), height (restricted to women with height 130-200 cm), nationality, pariety, civil status and smoking status.

<table>
<tr><td></td><td>
Number of patients in study population: 788,710
Number of patients excluded: 1218763 (data not available or did not meet height/weight criteria above)
Age:18-50
Males/females: all female

PART 2
Study Population: Men identified through the Swedish national inpatients register as having coeliac disease which led to an inpatient stay before or after conscription. In order to be eligible, data on weight (restricted to men with weight 30-200 Kg) and height (restricted to men with height 130-200 cm) had to be also available from the national conscripts register before 2000. Before 2000 most Swedish men were conscripted (80%-98% between 1996 and 2000). Data are reported for men diagnosed with coeliac disease before and after weight measurement – only the data for men diagnosed after weight measurement are eligible for the review and are reported below.
Control Population: Each patient was matched with up to 5 controls for age, sex, calendar period and country of residence. Controls were identified via a government total population register.
Number of patients in study population: 70 (1047 men with existing coeliac disease at the time of weight measurement were also included but not reported here)
Number of patients in control population: 6887
Number of patients excluded: 1218763 (data not available or did not meet height/weight criteria above)
Age:18-50
Males/females: all male
Country: Sweden
Other comments:
</td></tr>
<tr><td>Source of funding</td><td>Government and charity</td></tr>
<tr><td>Sign/Symptom</td><td>Body mass index</td></tr>
<tr><td>Reference standard</td><td>Inpatient stay related to coeliac disease as defined by international classification of disease codes (ICD-7: 286.00; ICD-8:269.00, 269.98, ICD-9: 579A; ICD-10: K90.0)</td></tr>
<tr><td>Results</td><td>
PART 1
<table>
<tr><th></th><th>With coeliac disease (n=174)</th><th>Without coeliac disease (n=787986)</th></tr>
<tr><td>BMI<18</td><td>29 (16.7%)</td><td>41100 (5.2%)</td></tr>
<tr><td>BMI 18-24.9</td><td>129 (74.1%)</td><td>574195 (72.9.%)</td></tr>
<tr><td>BMI >=25</td><td>16 (9.2 %)</td><td>172691 (21.9%)</td></tr>
</table>
</td></tr>
</table>

Regression adjusted for age parity, smoking, calendar period and civil status for predictive value of BMI<18 for coeliac disease: Adjusted HR =2.5 (95% CI 1.7-4.9)

PART 2

	With coeliac disease (n=70)	Without coeliac disease (n=6887)
BMI<18	10 (9.8%)	446 (6.5%)
BMI 18-24.9	50 (71.4%)	5449 (79.1%)
BMI >=25	10 (14.3 %)	992 (14.4%)

Regression adjusted for calendar period and socioeconomic group for predictive value of BMI<18 for coeliac disease: Adjusted OR =2.2 (95% CI 1.0-4.8)

Comments

PART 1:

The study population was limited to women who were pregnant – this may limit the generalizability of these findings to coeliac disease patients as a whole, and may introduce bias because the control participants were recruited from a general population register (not required to be pregnant). Coeliac disease was only identified if associated with an inpatient stay, potentially misidentifying some individuals with coeliac disease.

PART 2:

Case and control participants were matched for some baseline characteristics, limiting the impact of some confounding factors. However, only single sign/symptom was investigated, so there is still a high risk of confounding. Also the way that the populations were selected may mean that it does not reflect coeliac patients as a whole. For example, an inpatient stay was required for individuals to be identified as having coeliac disease, which may have biased the sample to more severe cases of coeliac disease. Conversely, participants were identified from a conscription register which may have biased the sample to less severe cases.

Paediatric studies

Bibliographic reference	Alehan, F., Ozcay, F., Erol, I., Canan, O., and Cemil, T. Increased risk for coeliac disease in paediatric patients with migraine. 2008. Cephalalgia 28(9), 945-949. 2008.
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? Yes, question clear 2. Cases and controls from comparable populations? 3. Same exclusion criteria used for both cases and controls? 4. What was participation rate for each group? Cases: controls: N/A; all blood tested. 5. Participants and non-participants are compared to establish their similarities or differences? Yes; baseline characteristics the same between groups. 6. Cases are clearly defined and differentiated from controls: cases are defined in terms of seropositivity, seropositive confirmed with biopsy 7. It is clearly established that controls are not cases? Clear in the fact that cases are seronegative, however this was not confirmed by biopsy 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? Yes, no person was to have had previous suspicion of CD or previous duodenal biopsy 9. Exposure status is measured in a standard, valid, and reliable way? Yes; serological testing for CD was standard 10. Main potential confounders are identified and taken into account in the design and analysis? Only single predictive factor considered other factors not taken into consideration 11. Have confidence intervals been provided? No; calculated from raw data
Study aim and type	To determine the prevalence of coeliac disease in paediatric patients with migraine UK
Patient characteristics	Study Population: attending child neurology outpatient clinic; May 2004 to January 2006 Control Population: with minor respiratory illness, no history of recurrent headache or gastrointestinal problems N=73, study group; - n=41 female, age 12.01±3.07yrs, n=30 had migraine with aura N=147, control group; - n=85 female, age 11.82±3.25yrs

	Inclusion: fulfilling the criteria for migraine according to the International Headache Society (all examined by the same child neurologist; complete physical and neurological examination; structured interview concerning characteristics of headache Exclusion: previous suspicion of coeliac disease
Sign/Symptom	Migraine
Investigations	Serum samples for tTGA antibody and IgA analysis - assay (Organtec Diagnostica GmbH ORG 540A; cut off level for a positive result, 10U/mL) Positive tTGA – endoscopic duodenal biopsy for confirmation of coeliac disease
Results	All participants and controls had normal serum IgA levels Positive tTGA antibodies; - N=4/73 (5.5%) study group, N=1/147 (0.7%) control group, p=0.043 Biopsy; - N=3/3 study group, all considered to show potential coeliac disease (N=1 in the study group and N=1 in the control group declined a biopsy)
Funding	Research grant from Baskent University
Other comments	

Bibliographic reference	El-Hodhod, M., El-Agouza, I., Abdel-Al, H., Kabil, N., and Bayomi K. Screening for celiac disease in children with dental enamel defects. 763783, 2012
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? question clear 2. Cases and controls from comparable populations? Yes - matched for baseline characteristics. 3. Same exclusion criteria used for both cases and controls? No - 1482 children presented with DED- not clear why only 140 enrolled in study 4. What was participation rate for each group? All recruited participants from both groups reported to have participated 5. Participants and non-participants are compared to establish their similarities or differences? Yes 6. Cases are clearly defined and differentiated from controls: yes; seropostivity 7. It is clearly established that controls are not cases? Yes, however no biopsy 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? All patients recruited in same way with no prior knowledge of coeliac status 9. Exposure status is measured in a standard, valid, and reliable way? Yes 10. Main potential confounders are identified and taken into account in the design and analysis? No- other factors that contribute to DED I.e diet, socio economic status, not accounted for. 11. Have confidence intervals been provided? No - calculated from raw data
Study aim and type	To detect the frequency of coeliac disease among patients with dental enamel defects Egypt
Patient characteristics	Study Population: with dental enamel defects, recruited from attendees of general and dentistry paediatric clinics who showed any abnormality in teeth structure or shape Control Population: age and sex matched, recruited among normal children coming for routine check-up in children's hospital in the well child clinic N=140, study group; - n=68 (48.6%) female, age range 4-12yrs, mean age 8.33±1.73yrs N=720, control group; - n=349 (48.5%) female, age range 4-12yrs Inclusion: with dental enamel defects, aged between 4 and 12yrs

	Exclusion: chronic illness other than gastrointestinal symptoms, on inhalation therapy for bronchial asthma NS differences between groups for age or gender. Higher percentage of consanguinity in the study group (42.86%) compared with the control group (23.47%), p<0.0001
Sign/Symptom	Dental enamel defects
Investigations	Oral examination for hard tissue changes by a paediatric dentist; evaluated under good artificial light using dental mirros, dental probes and sterile gauze without excess drying. Dental examination in accordance with FDI criteria. A single defect measuring less than 1mm in diameter was not recorded. In case of doubt about the existence of a defect it was scored as normal. Opacities were differentiated from white spot carious lesions, based on colour, texture, demarcation, and relationship to gingival margin. The enamel defects affecting deciduous and permanent teeth were graded 0 to IV according to Aine's classification. They were followed up for oral hygiene and problematic defects were treated. Coeliac disease; - IgA and IgG tTGA; ELISA (Orgentec) - According to manufacturer instructions a value above 10U/mL was used as a cutoff value - Total serum IgA was measured - Positive serology – oesophagogastroduodenoscopy and intestinal biopsy from the second part of the duodenum (minimum 4 biopsies) assessed histopathologically for features of coeliac disease
Results	(this study included a 1-yr follow-up of dental care and gluten free diet – data not reported in this evidence table) Coeliac disease; - Dental enamel defects group, n=25 (17.9%) - Control group, n=7 (0.97%) - X^2 36.95, p<0.0001 Recurrent gastrointestinal symptoms; - Dental enamel defects group, n=25 (17.9%) - Control group, n=146 (20.3%) - NS difference

	Underweight; - Dental enamel defects group, n=45 (32.1%) - Control group, n=41 (5.7%) - X^2 57.94, p<0.0001
Funding	Not reported
Other comments	

Bibliographic reference	Inaloo, S., Dehghani, S. M., Farzadi, F., Haghighat, M., and Imanieh, M. H. A comparative study of celiac disease in children with migraine headache and a normal control group. 20110823. Turkish Journal of Gastroenterology 22(1), 32-35. 2011.
Study aim and type	To assess the prevalence of coeliac disease in children with migraine headache Iran
quality	**NICE case-control quality checklist** 1. The study addresses an appropriate and clearly focused question? question clear 2. Cases and controls from comparable populations? Yes - matched for baseline characteristics. 3. Same exclusion criteria used for both cases and controls? Unclear; no clear exclusion criteria. Uncelar whether consecutive recruitment 4. What was participation rate for each group? All recruited participants from both groups reported to have participated 5. Participants and non-participants are compared to establish their similarities or differences? Yes 6. Cases are clearly defined and differentiated from controls: yes; seropostivity 7. It is clearly established that controls are not cases? Yes, however no biopsy 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? All patients recruited in same way with no prior knowledge of coeliac status 9. Exposure status is measured in a standard, valid, and reliable way? Yes 10. Main potential confounders are identified and taken into account in the design and analysis? No confounding factors taken into account 11. Have confidence intervals been provided? No - calculated from raw data
Patient characteristics	Study Population: paediatric neurology clinic Control Population: participating in another study for detection of the prevalence of coeliac disease N=100, study group; - n=41 (41%) female, mean age 10.6±2.8yrs, range 5-18yrs, 30% migraine with aura, < x3/mth in 63% of cases, duration 3-72hrs (60% of participants), 75% had a history of migraine headache in first-degree relatives N=1500, control group; - n=675 (45%) female, mean age 9.5±1.3yrs Inclusion: diagnosis of migraine according to the HIS criteria

Sign/Symptom	Migraine
Investigations	General and neurological physical examinations by paediatric neurologist Serum IgA and IgA tTGA (Diagnostocs GmbH), tires above 18U/mL considered to be positive Positive serology – duodenal biopsy, definite diagnosis based on histologic criteria
Results	Positive tTGA antibodies; - N=2/100 study group, N=30/1500 (2%) control group Biopsy; - N=2/2 study group – confirmed the diagnosis of coeliac disease
Funding	Not reported
Other comments	

D.2 Review question 4.2

Addison's disease

Bibliographic reference	**Fichna et al. (2010)**
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=85 adults with autoimmune Addison's disease
Study population	Inclusion: patients with autoimmune Addison's disease: Mean age: 48 ± 14.9 years (from 18 to 82); 61 females, 24 males; Mean age at Addison's onset: 34.6 ± 12.6 years (significantly earlier in males)
Control	none
Details of coeliac testing	tTG IgA
Results	3.5% (3/85) were serologically positive Only one was confirmed as positive on biopsy giving a 1.1% (1/85) rate of biopsy-confirmed CD in Addison's disease
Source of funding	The Polish Ministry of Science and Higher Education gave partial support in the form of grants
Conflicts of	Not reported

interest	
Comments	None

Arthritis

Bibliographic reference	**Atzeni et al. (2008)**
Study type	Case series
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=20 patients with active rheumatoid arthritis N=50 healthy controls
Study population	Inclusion: patients with active rheumatoid arthritis fulfilling ACR classification criteria for RA and who were being treated with adalimumab and methotrexate (13 also had corticosteroids and 14 NSAIDs) Mean age: 58.5 years (range 28 to 80); 17 women, 3 men; Mean disease duration: 8.6 ± 12.3 years
Control	None
Length of follow-up	Patients tested at baseline and after 6 months of treatment for arthritis
Details of coeliac testing	Anti-tTG (ELISA: Phadia, Frieburg, Germany) – IgA and IgG CD confirmed on biopsy
Results	1 patient (5%) had positive tTG IgA and biopsy-confirmation (both at baseline and at follow-up; anti-tTG IgG was negative for all patients)

	(however, anti-tTG IgG levels were elevated during treatment and higher in the study group than among healthy controls both at baseline [p=0.028] and 6 months of treatment [p=0.001])
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Coacciloli et al. (2010)**
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=93 patients with rheumatoid or psoriatic arthritis or psoriasis
Study population	Inclusion: patients undergoing treatment under physicians and dermatologists at the Santa Maria Hospital in Terni since July 2006 until October 2008 with rheumatoid or psoriatic arthritis or psoriasis (all were on DMARD therapy) Median age: 55 years (range 8-84) 53 males, 40 females N=15 had rheumatoid arthritis: 6 males with mean age 59 years (32-76); 9 females with age 53 years (42-69)

	N=27 had psoriatic arthritis: 13 males with mean age 58 years (43-73); 14 females with age 57 years (25-81) N=51 had psoriasis: 34 males with mean age 56 years (28-80); 17 females with age 52 years (8-72)
Control	None
Length of follow-up	n/a
Details of coeliac testing	EMA (substrate of monkey oesophagus: Biosystems, SA, Barcelona, Spain) and anti-tTG IgA (ELISA: Diamedix Co. subsidiary of IVAX Diagnostics Inc, Miami, Fl, USA) and serum Ig Those positive had biopsy
Results	Biopsy-confirmed CD: 0% with RA 0% with psoriatic arthritis were positive 5.9% (3/51) with psoriasis
Source of funding	Not reported
Conflicts of interest	Paper reports that none were declared
Comments	

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

Bibliographic reference	**Francis et al. (2002)**
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	UK

Number of patients	N=160 adults with rheumatoid arthritis
Study population	Inclusion: consecutive patients with rheumatoid arthritis attending the rheumatology outpatients, mean age 61yrs (range 20 to 84yrs), N=107 (67%) female, mean disease duration 12yrs
Control	
Results	N=1 with CD, which had been previously diagnosed, prevalence of CD in RA 0 (95% CI; 0 to 24%)
Source of funding	Rheumatology Fund, Lincoln County Hospital, Postgraduate Medical federation, Lincoln
Conflicts of interest	
Comments	

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

Arthritis, Juvenile

Bibliographic reference	**George et al. (1996)**
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	Netherlands
Number of patients	N=62 children with juvenile chronic arthritis
Study population	Inclusion: children with juvenile chronic arthritis (JCA) being followed at 3 departments of paediatric rheumatology during 1993 and 1994, N=36 female, mean age 9.9±3.5SD (range 3.3 to 16.8yrs), IgG AGA used in one case of IgA deficiency

Results	N=8 with at least 1 +ve screening test, N=5 biopsed, N=4 normal biopsy Frequency of coeliac disease 1.5%
Source of funding	Not stated
Conflicts of interest	
Comments	

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

Bibliographic reference	**Lepore et al. (1996)**
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=119 children with juvenile chronic arthritis
Study population	Inclusion: children with juvenile chronic arthritis being treated at two centres for paediatric rheumatology, mean age 11.5yrs (range 2 to 16yrs), N=87 female
Results	N=4 (3.3%) AEA +ve, N=3 biopsy +ve for CD
Source of funding	Not reported
Conflicts of	

interest	
Comments	

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

Bibliographic reference	**Robazzi 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? YES (All patients tested) 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
Country	Brazil
Number of patients	N=43 children with juvenile idiopathic arthritis N=18 healthy patients
Study population	Inclusion: outpatients at two paediatric rheumatology services between January 2008 and January 2010 with juvenile rheumatoid arthritis 25 girls, 28 boys Age at diagnosis: 7.5 ± 3.8 years (range 1.1-15.9) Age at study: 10.4 ± 4.0 years (range 2.3-17.9) Disease duration: 41.3 ± 37 months (range 2-156)
Control	2 control groups of healthy outpatient paediatrics matched by sex and age at a 1:3 ratio (none had signs of any chronic disease)
Length of follow-up	n/a
Details of coeliac testing	Anti-tTG IgA (ELISA; reference < 7 U/ml, Orgentec, Diagnostika) Jejunal biopsy to confirm diagnosis if positive serology (p = 0.56)

Results	Only one patient (2%) has positive serology and biopsy confirmed CD (typical villous atrophy and crypt hyperplasia) None in control group had positive serology.
Source of funding	
Conflicts of interest	
Comments	The study also reported on 66 patients with rheumatic fever but as this condition was not in the review protocol, details on these patients were not extracted

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

Cardiomyopathy in adults

Bibliographic reference	**Chicco et al. (2010)**
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=104 adults with idiopathic dilated cardiomyopathy N=63 diseased controls N=101 healthy controls
Study population	Inclusion: adults patients with idiopathic dilated cardiomyopathy who underwent screening between April 2007 and February 2008 Characteristics of those with idiopathic dilated cardiomyopathy: 59 males/45 females, median 52 years (range 28-61)
Control	Diseased controls: 43 males/20 females, median 59 years (range 39-72) Healthy controls: apparently healthy nurses and residents working in cardiology or paediatric departments: 60 males/41 females,

	median 40 years (range 27-50)
Details of coeliac testing	IgA anti-tTG (Eu-tTG Quick, Eurospital, Italy) IgA and IgG serum (ELISA, Eu-tTG IgG, human IgA, Eurospital, Italy) EMA IgA (immunofluorescence assay on human umbilical cord cryosections) Biopsy for all with positive anti-tTG or EMA
Results	2.9% (3/104) with idiopathic dilated cardiomyopathy had biopsy-confirmed CD (Marsh type IIIc; 2 males, 1 female) 0% (0/63) diseased controls 1% (1/101) of controls had biopsy-confirmed CD (Marsh type IIIc)
Source of funding	Institute of Child Health IRCCS “Burlo Garofolo” Trieste
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**de Menzes et al. (2012**
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=56 children and adolescents with dilated cardiomyopathy or myocarditis
Study population	Inclusion: children and adolescents with a clinical diagnosis of dilated cardiomyopathy or myocarditis who were seen at a paediatric

	cardiology service between December 2009 and November 2010; children were older than 1 (to ensure gluten exposure) Exclusion: previous CD diagnosis Median age 96 months (from 12 to 225 months / 1 and 18 years) 57% (32) female
Control	None
Details of coeliac testing	EMA IgA (Immco Diagnostics, Genbiotech; > 20 U/ml were positive) tTG IgA (Orgentec, Diagnostika; > 10 U/ml were positive) Serum IgA was also determined to rule out IgA deficiency intestinal biopsy if positive serology
Results	Only one had tTGA serum positive levels and also had intraepithelial lymphocytosis and total villous atrophy. 1.8% (95% CI 0.04-9.5%) were biopsy-confirmed CD
Source of funding	Not reported
Conflicts of interest	Study reports none related to this article
Comments	

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

Bibliographic reference	**Frustaci et al. (2002)**
Study type	Case-control
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
Country	Italy
Number of patients	N=187 adults
Study population	Inclusion: consecutive patients with myocarditis admitted with either heart failure (N=110), with cardiac arrhythmias (N=77), N=118 male, mean age 41.7±14.3yrs, none had IgA deficiency
Control	none
Details of coeliac testing	
Results	N=13 +ve IgA-tTG N=9 +ve for AEA and had iron-deficiency anaemia and had histologic evidence of coeliac disease Prevalence of coeliac disease 4.4% with myocarditis vs. N=1 (0.3%), p<0.003
Source of funding	MURST project
Conflicts of interest	
Comments	

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

Bibliographic reference	**Vizzardi et al. (2008)**
Study type	Cross-sectional data from case series
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
Country	Italy
Number of patients	N=350 with idiopathic or ischaemic dilated cardiomyopathy
Study population	Patients: consecutive patients referred to the Heart Failure Centres of the Cardiology Department of a hospital from April to December 2005 who were unaware of a CD diagnosis at enrolment N=182 idiopathic dilated cardiomyopathy; mean 52 ± 12 years; 128 male, 54 female N=168 ischaemic dilated cardiomyopathy; mean 64 ± 14 years; 130 male, 38 female (patients were significantly different in terms of age [p<0.0001] and ejection fraction [p<0.005])
Control	none
Details of coeliac testing	tTG antibody (CELIKEY^{TM} with human recombinant antigen, Pharmacia&Upjohn, Sweden; > 7 U/ml cut-off value) and EMA (immunofluorescence on monkey oesophagus slides, Antiendomysium®, Eurospital, Italy) for those tTG positive Biopsy for those serologically positive (using Marsh classification)
Results	0**.6% (2) tested positive for tTG and EMA antibodies; both patients had complete villous atrophy on biopsy** Both had been on optimized therapy for heart failure for > 2 years
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Down syndrome

Bibliographic reference	**Bonamico 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? 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
Country	Italy
Number of patients	N=1202 with Down's Syndrome (N=1110 children, N=92 adults)
Study population	Inclusion: consecutively enrolled patients with Down's Syndrome enrolled by the Italian Society of Paediatric Gastroenterology and Hepatology and the Clinical Genetics Group of the Italian Society of Paediatrics, N=1110 children; aged 15mths to 18yrs, N=92 adults; 18 to 46yrs, N=609 males, N=593 females
Results	N=55 (N=48 children, N=7 adults)(4.6%) with CD N=55 with CD had higher percentages of those with growth failure ($p<0.001$), anorexia ($p<0.01$), constipation ($p<0.05$), and higher frequency of cases of low haemoglobin, low serum iron and low calcium ($p<0.01$) than in N=55 who were IgA AGA +ve and IgA EMA –ve, and then N=57 IgA AGA –ve and IgA EMA –ve N=38 (69%) classic CD, N=6 (11%) atypical symptoms, N=11 (20%) silent CD
Source of funding	Not stated
Conflicts of interest	
Comments	

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

Bibliographic reference	**Cerqueria et al. (2010)**
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=98 patients with Down syndrome
Study population	Inclusion: patients with Down syndrome living in the north of Portugal and screened for CD between January 2005 and December 2006 58 male, 40 female; 51 children and adolescents (aged 1-19); 47 adults (aged 20-45)
Control	None
Length of follow-up	n/a
Details of coeliac testing	IgA EMA (immunofluorescence assay with monkey oesophagus as substrate, Byosystems, Middletown, Conneticut, USA; serum was diluted to 1:5 and results were ositive when green network pattern under fluorescent microscope was observed) IgA tTG (Enzyme-linked immunosorbent assay with tissue translugtaminase as antigen, Quanta Life, Inova, Livermore, California, USA; results higher than 20 U/ml were considered positive) Total IgA serum level to exclude IgA deficiency Those serologically positive had biopsy. CD was diagnosed if positive serology and Marsh III on biopsy.
Results	19.4% (19/98) were positive for IgA EMA – 9 children and 10 adults 12.2% (12/98) were positive for IgA anti-tTG (all were also positive for IgA EMA) None had abnormal IgA values The parents of 2 patients did not consent to upper endoscopy. On biopsy, 7 had Marsh I, 1 had normal mucosa, Marsh III was confirmed in 9 (4 of these had severe villous atrophy – Marsh IIIB and IIIC, and 5 had partial villous atrophy – Marsh IIIA) **9.2% (9/98) prevalence rate of histologically confirmed CD** One child had a growth deficit (weight percentile < 5), no adult CD patient was underweight (BMI < 19.9), one adolescent and 4 adults patients were obese (BMI ≥ 30)

Source of funding	Paper reports 'none declared'
Conflicts of interest	Paper reports that the authors declared no conflicts of interest
Comments	

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

Bibliographic reference	**Goldacre et al. (2004) [**
Study type	Case-control
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	UK
Number of patients	N=1453 N=460000 control
Study population	Inclusion: data from the Oxford Record Linkage Study, this includes brief statistical abstracts of records of all hospital admissions, including day cases in the NHS and all deaths wherever they occurred, in defined populations within the former Oxford NHS region from January 1963 to March 1999, the Down's syndrome cohort obtained from statistical records, the reference cohort from records of admission for other medical and surgical conditions, N=937 0 to 14yrs, N=516 15 to 59yrs
Control	
Results	Results for cancers and other immune conditions not reported here N=4 with coeliac disease observed in the Down's cohort, expected number N=0.9, Adjusted risk ratio 4.7 (CI: 1.3 to 12.2)
Source of funding	Oxford Health Authority, Research and Development Directorate at the Department of Health

Conflicts of interest	
Comments	

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

Bibliographic reference	**Pavlović et al. (2012)**
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? 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
Country	Serbia
Number of patients	N=91 children with Down's Syndrome
Study population	Inclusion: children with Down's Syndrome evaluated at a paediatric department between October 2004 and January 2011. 50 boys, 41 years; Mean age 6.3 years (range 8 months to 16 years)
Control	none
Details of coeliac testing	Serum IgA IgA tTG and IgG tTG (ELISA, Orgentec Diagnostika; 10 U/ml or greater were positive) IgG EMA (indirect immunofluorescence with primate oesophagus substrate, IMMCO Diagnostics) Biopsy if positive serology
Results	Of 5 with serum IgA deficiency, IgG EMA was negative for all but IgG tTG was positive in 3.Biopsy was normal for all 3. Of 5 patients with positive IgA tTG, 4 had positive biopsy for CD giving a biopsy-confirmed CD rate of 4.4% (95% CI, 1.7-10.7%) (Marsh

	3a, 3b or 3c)
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Wouters et al. (2009)**
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? 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
Country	Netherlands
Number of patients	N=155 children with Down's Syndrome
Study population	Inclusion: children who visited a special Down's Syndrome outpatient clinic at a mixed secondary and tertiary referral centre from May 2005 to June 2007 Mean and SD: Age 7.4 ± 4.6 (from 2 months to 19 years); 97 male, 58 female
Control	None
Length of follow-up	n/a
Details of coeliac	HLA-DQ typing

testing	EMA and TGA antibodies tested in those with HLA-DQ2 or 8 IgA deficiency was tested for using ELISA method using *Escherichia coli* IgA In those <2 years, AGA IgA was also measured If EMA-TGA tests were positive a small intestinal biopsy was performed to confirm the diagnosis
Results	63/155 had HLA-DQ2 or HAL-DQ8 Of these 63, 8 had positive serology for EMA/TGA (overall prevalence: 5.1%) **Overall biopsy-confirmed CD prevalence: 4.5% (7/155)** (one patient did not have a biopsy)
Source of funding	Not reported
Conflicts of interest	Paper reports that the authors declared no conflicts of interest
Comments	

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

Epilepsy or seizures

Bibliographic reference	**Cronin et al. (1998)**
Study type	Case control
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	Ireland
Number of patients	N=177 adults N=488 control group
Study population	Inclusion: patients attending a seizure clinic of a university hospital, N=80 male, N=97 female, N=80 male, mean age 36yrs (range 14 to

	80yrs), median age at onset of epilepsy was 14yrs (range 1 to 63yrs)
Controls	Control group from patients attending an ante natal clinic
Results	N=4 EMA +ve, +ve for coeliac disease on biopsy, frequency of CD 1:44 (control N=2 EMA +ve, frequency of CD 1:244)
Source of funding	Not reported
Conflicts of interest	
Comments	

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

Bibliographic reference	**Djurić et al. (2010)**
Study type	Comparative 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	Serbia
Number of patients	N=125 children with idiopathic epilepsy N=150 healthy children
Study population	Inclusion: 72 girls, 53 boys mean age 10.51 ± 3.53 (range 2 to 18 years)

Control	Healthy children
Details of coeliac testing	Serum IgA (radioimmunodiffusion) IgA tTG with human recombinant tTG (ELISA, Euroimmun) Endoscopic small bowel biopsy if serologically positive (CD confirmed with ESGHAN recommendations)
Results	3 with epilepsy had positive IgA tTG but only one (0.8%) had biopsy-proven CD (Marsh IIIa; others Marsh 0) 1 (0.6%) in control group had positive IgA tTG and positive biopsy (Marsh IIIa) (difference p>0.05)
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Peltola et al. (2009)**
Study type	Case control
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
Country	Finland
Number of patients	N=48 patients with therapy-resistant, localisation-related epilepsy N=71 healthy blood donors
Study population	Inclusion: patients with therapy-resistant, localisation-related epilepsy (>1 seizures/month despite prior treatment with at least 2 antiepileptic drugs) attending an outpatient clinic All were on antiepileptic medication (13 monotherapy, 35 polytherapy)

<table>
<tr><td></td><td>One in each group had concomitant autoimmune disorders (systematic lupus erythematosus, Sjögrens syndrome, Henoch-Schönlein syndrome; none had T1D)
One patient had a prior diagnosis of CD (this patient did not have a biopsy)

<table>
<tr><th></th><th>Temporal lobe epilepsy with hippocampal sclerosis (n=16)</th><th>Temporal lobe epilepsy without hippocampal sclerosis (n=16)</th><th>Extratemporal epilepsy (n=16)</th></tr>
<tr><td>Mean age (range) (years)</td><td>42 (24/60)</td><td>43 (17-63)</td><td>44 (17-64)</td></tr>
<tr><td>Number female/male</td><td>10/6</td><td>7/9</td><td>6/10</td></tr>
<tr><td>Mean duration of epilepsy in years (range)</td><td>27 (12-47)</td><td>29 (10-61)</td><td>33 (3-45)</td></tr>
<tr><td>Mean seizure frequency (mean per month [range])</td><td>3 (1-10)</td><td>3 (1-25)</td><td>6 (1-30)</td></tr>
</table>
</td></tr>
<tr><td>Control</td><td>Consecutive healthy blood donors</td></tr>
<tr><td>Details of coeliac testing</td><td>IgA EMA antibodies (indirect immunofluorescence method using human umbilical cord as substrate)
IgA anti-tTG antibodies (Quanta Lite tTG ELISA, INOVA Diagnostics, Inc, San Diego, CA; > 20 AU were considered positive)
IgA and IgG AGA with standard enzyme immunoassay with crude gliandin antigen (G3375, Sigma, St Louise MO, USA; lower limit of positivity for IgA was 0.2 AU/ml and 10 AU/ml for IgG)
CD defined as severe partial or subtotal villous atrophy with crypt hyperplasia in the small bowel and subsequent clinical, serological or histological recovery on a GFD</td></tr>
<tr><td>Results</td><td>4.2% (2) had biopsy confirmed CD
(table in the study says 3 had CD but the text says 2 have CD and one did not have biopsy)

Of the 2 patients with biopsy-confirmed CD:
- one patient with normal bowel histology but immunohistochemical findings suggesting CD and who subsequently developed severe partial villous atrophy with crypt hyperplasia
- one had severe villous atrophy with crypt hyperplasia
- both had had temporal lobe epilepsy with hippocampal sclerosis

None of the controls had biopsy-confirmed CD</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Conflicts of interest</td><td>Paper reports that there were none</td></tr>
<tr><td>Comments</td><td></td></tr>
</table>

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

Bibliographic reference	**Pratesi et al. (2003)**
Study type	Case control
Study quality	
Country	Brazil
Number of patients	N=255 patients with epilepsy N=4405 control
Study population	Inclusion: adults and children with epilepsy attending 2 clinics, N=119 children; N=49 female, mean age 7.97yrs, median age 8yrs (range 1 to 14yrs), N=136 adults; N=64 female, mean age 30.27yrs, median age 29yrs (range 15 to 65yrs)
Control	N=2034 children, N=2371 adults
Results	N=2/255 (N=1 adult, N=1 child) with coeliac disease; 1:127 Control N=15/4405 with coeliac disease; 1:293
Source of funding	Not reported
Conflicts of interest	
Comments	

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

Dyspepsia

Bibliographic reference	**Giangreco et al. (2008)**
Study type	Comparative 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	The Netherlands
Number of patients	N=726 adults patients with dyspepsia
Study population	Inclusion: consecutive patients with unexplained prolonged dyspepsia from 5413 patients who underwent esophago-gastro-duodenoscopy between January 2005 and June 2007 Exclusion: family history of CD, pathologies associated with CD, patients with GORD 282 male, 44 female; mean age 39.6 years (18-75) 14% (102) had ulcer-like dyspepsia, 47.4% (344) dysmotility-like dyspepsia, 38.6% (280) with indeterminate dyspepsia
Control	Comparisons were made between those with and without CD
Length of follow-up	n/a
Details of coeliac testing	Biopsy (classified according to Marsh-Oberhuber criteria) Anti-tTG and anti-EMA
Results	On endosccopy: 61% 9444) had normal endoscopic findings 20.5% (149) had peptic lesions 1.1% (8) had CD diagnosed on endoscopy 0.5% (4) had malignancy 16.7% (121) had miscellaneous (including lymphocytic gastritis, etc) On biopsy: 2% (15) were diagnosed with CD (5 male, 10 female; mean age 39.9 years from 20-61) - 5 had Marsh IIIc - 8 had Marsh IIIb - 2 had Marsh IIIa There were no significant differences between those with and without a diagnosis of CD in terms of sex, age, and type of dyspepsia - sex: OR 1.28, 95%CI 0.45-3.60 (p=0.6) - mean age: OR 1.86, 95% CI 0.71-4.65 (p=0.3) - dysmotility-like dyspepsia: OR 1.27, 95% CI 0.47-3.42 (p=0.6) - indeterminate dyspepsia: OR 2.21, 95% CI 0.82-5.97 (p=0.1)
Source of funding	Not reported
Conflicts of	Not reported

interest	
Comments	

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

Irritable bowel syndrome

Bibliographic reference	**Cash et al. (2011)**
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? 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
Country	USA
Number of patients	N=492 adult patients with suspected irritable bowel syndrome N=458 asymptomatic individuals
Study population	Inclusion: patients with symptoms suggestive of non-constipated inflammatory bowel syndrome (NC-IBS) who presented to 4 sites from 2003 to 2008 who did not have alarm features suggestive or organic disease (ie. unexplained weight loss, fever, significant GI bleeding or historical features such as family history of a first degree relative with colon cancer, CD, or IBD); patients fulfilled Rome II criteria for IBS based on their responses to a questionnaire administered at the clinic Exclusion: previous diagnosis with co-morbid conditions that could have explained their GI symptoms (ie. CD, colon cancer, IBD, scleroderma, small intestinal bacterial overgrowth, uncontrolled thyroid disease or diabetes), previous GI or intestinal surgery (large or small bowel) (except appendectomy or cholecystectomy); patients with alarm features, women who were pregnant or breast-feeding, patients who had undergone previous diagnostic testing for the IBS symptoms Patient characteristic:

	Suspected IBS (n=492)	Healthy controls (n=458)	p value

<table>
<tr><td></td><td>
<table>
<tr><td>Age (SD)</td><td>40.72 (12.94)</td><td>54.44 (7.81)</td><td><0.0001</td></tr>
<tr><td>Proportion female</td><td>69.92% (344)</td><td>41.27% (189)</td><td><0.0001</td></tr>
</table>
The study also reported that significantly more patients in the suspected IBS group were Hispanic (4.27% vs 1.53%, p=0.01) and significantly more patients in the suspected IBS group were single (ie. not married)(22.15% vs 14.41%, p=0.001; 64.43% vs 74.89% were married, p=0.001)</td></tr>
<tr><td>Control</td><td>Patients who underwent colonoscopy for cancer screening or polyp surveillance (all controls completed the Rome II questionnaire to rule out IBS; patients with IBS symptoms, a history of colorectal cancer or other organic GI disease were not eligible)</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Details of coeliac testing</td><td>Serological tests (any test above the reference range was considered positive):
AGA IgG ELISA (reference range: < 10 U/ml)
AGA-IgA (reference range < 5/U/ml)
anti-human tTGA ELISA (reference range < 4 U/ml)
EMA IgA indirect immunofluorescence assay using monkey oesophagus as the substrate with reference range negative
Total serum IgA by nephelometry (reference range 44-441 mg/dl)

HLA-DQ2 and HLA-DQ8 were determined on PCR amplification and 72 probe hybridizations for the detection of allelic variants using proprietary methods

CD was defined as abnormal antibody test result and duodenal mucosal histology demonstrating villous atrophy and/or increased IELs</td></tr>
<tr><td>Results</td><td>Proportion of abnormal serological tests:
<table>
<tr><th></th><th>Suspected IBS (n=492)</th><th>Healthy controls (n=458)</th><th>p value</th><th>OR (95% CI)</th></tr>
<tr><td>Any abnormal serological test</td><td>7.3% (36)</td><td>4.8% (22)</td><td>0.25</td><td>1.49 (0.76, 2.90)</td></tr>
<tr><td>AGA IgG</td><td>4.9% (24)</td><td>3.0% (14)</td><td>0.70</td><td>1.19 (0.50, 2.79)</td></tr>
<tr><td>AGA IgA</td><td>1.6% (8)</td><td>1.8% (0.54)</td><td>0.54</td><td>1.41 (0.47, 4.22)</td></tr>
<tr><td>EMA</td><td>0.6% (3)</td><td>0.4% (2</td><td>0.66</td><td>1.65 (0.17, 15.42)</td></tr>
<tr><td>TTG IgA</td><td>1.2% (6)</td><td>0.4% (2)</td><td>0.15</td><td>3.87 (0.61, 24.74)</td></tr>
<tr><td>Total IgA (low)</td><td>0.6% (3)</td><td>0.7 (3)</td><td>0.93</td><td>0.93 (0.19, 4.62)</td></tr>
</table>
CD was confirmed on biopsy in 0.42% (4) of all study patients:
- 0.41% (2/492) with IBS
- 0.44% control group (2/468)
(p > 0.99; Fisher’s exact test)</td></tr>
<tr><td>Source of funding</td><td>Prometheus Laboratories, La Jolla, CA (who performed the testing) supported a study coordinator, NIH grant for one author</td></tr>
</table>

Conflicts of interest	22 authors have served as consultants to Prometheus Laboratories and another author is on the Speaker's Bureau of Prometheus Laboratories; all other authors have no conflicts of interest
Comments	

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

Bibliographic reference	**Cristofori, F. (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	Patients who presented at the paediatric department of University hospital Bari, Italy, for the diagnosis and follow-up of GI disorders consecutively referred for recurrent abdominal pain All children were managed according to the Rome III criteria. 992 children were evaluated; 782 were eligible; and 270 were diagnosed with IBS (201 with dyspepsia; 311 with functional abdominal pain) Exclusion criteria: • Functional gastrointestinal disorders • Gastroesophageal reflux disease • Gastritis • Lactose intolerance • Parasitosis • Inflammatory bowel disease

Co-existing condition	Irritable Bowel syndrome (IBS)
Investigations	Serum concentrations of IgA, IgA tTG, and EMA were tested and a duodenal biopsy was performed in the case of elevated serum antibodies Biopsy specimens were graded according to the Marsh criteria. Final diagnosis of CD was made on the presence of positive antibodies, positive HLA status, and villous atrophy (Marsh 3).
Results	12/270 patients with IBS had CD diagnosis (a further 3 with positive Iga tTG did not have histological evidence of CD). Prevalence = 4.4% (95% CI: 2.5 - 7.6)
Funding	Not listed
Other comments	None

Bibliographic reference	**El-Salhy et al. (2011)**
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	Norway
Number of patients	N=968 adults with irritable bowel syndrome

Study population	Inclusion: patients referred to the gastroenterology section of the Stord Helse-Fonna Hospital between December 2005 and December 2010 and that satisfied the Rome III criteria for IBS; those between 18 and 60 without organic gastrointestinal disease or clinical significant system disease Exclusion: pregnant women, those who had undergone abdominal surgery (except appendectomy, caesarean section or hysterectomy), patients with a history of mental retardation Mean 32 years old (range 18-59) 95% females
Control	n/a
Length of follow-up	n/a
Details of coeliac testing	Histopathological examination on gastroscopy and immunohistochemistry Anti-tTG IgA with mouse anti-human leucocytes CD45 (Dako, no.IS751) and second layer with biotinylated mouse anti-IgG (Dako)
Results	All but 7 had normal histology on biopsy. - 6 had Marsh 1 but subsequent biopsy after 3-6 months and 8 new biopsies revealed 3 were normal on histology and negative anti-tTG IgA an 3 with Marsh I had similar second biopsies and positive anti-tTG IgA - 1 had Marsh 3b Overall 4 patients (0.4%) were diagnosed with CD (1 had Marsh 3b and 3 had Marsh 1; aged 24, 20, 36 and 38 years)
Source of funding	Helse-Fonne grant
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Sanders et al. (2001)**
Study type	Case control
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	UK
Number of patients	N=300 adults with IBS N=300 healthy matched controls
Study population	Inclusion: consecutive patients who fulfilled Rome II criteria for IBS
Controls	Age and sex matched healthy controls
Length of follow-up	None
Details of coeliac testing	IgG AGA, IgA AGA, EMA Biopsy if serologically positive
Results	22% (66) had positive serology 4.7% (14) of these patients had biopsy-confirmed CD vs 0.67% (2) controls who had both positive serology and biopsy-confirmed CD OR 7.0 (95% CI 1.7-28.0) (p=0.004)
Source of funding	
Conflicts of interest	
Comments	

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

Bibliographic reference	**Sanders et al. (2003)**
Study type	Cross-sectional data
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	UK
Number of patients	N= 1200 volunteers (123 with IBS)
Study population	Inclusion: volunteers over the age of 16 years who were recruited from January 1999 to June 2001 from 5 GP practices in South Yorkshire were screened for CD; those with IBS fulfilled the ROME II criteria for IBS
Controls	None
Length of follow-up	n/a
Details of coeliac testing	IgG/IgA AGA (ELISA) and EMA (indirect immunofluorescence using monkey oesophagus substrate and fluorescein isothianate conjugate-conjugated anti-human IgA [alpha chain specific, monkey absorbed] antibody) If positive for IgA AGA, EMA, or IgG if IgA deficient, biopsy was performed (using revised Marsh classification)
Results	3.3% (4/123; 95% CI 0.1-0.6%) of participants with IBS had biopsy-confirmed CD
Source of funding	Action Research
Conflicts of interest	The primary author is a training fellow for the Action Research
Comments	Study reported the overall prevalence of CD; patients were followed up to determine the affects of a GFD but this was not excluded here

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

Other Gastrointestinal conditions

Bibliographic reference	**Aziz et al. (2010)**
Study type	Cross-sectional data from case series
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	UK
Number of patients	N=100 patients with lymphocytic duodenosis
Study population	Inclusion: patients with lymphocytic duodenosis (>25 IELs per 100 enterocytes) seen sequentially at a tertiary care centre for gastroenterology between February 2003 and 2010 75 women; median age 47 years (16 to 83 years)
Control	none
Length of follow-up	18 months (range 2-72)
Details of coeliac testing	EMA or tTG and duodenal biopsy (CD was diagnosed if positive serology, relevant symptoms, HLA pattern of DQ2 or DQ8, progression to villous atrophy or persistence of lymphocytic duodenosis, symptomatic response to GFD)
Results	16% (16) were found to have CD
Source of funding	Not reported
Conflicts of interest	Paper reports no personal and funding interests
Comments	

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

Bibliographic reference	**Casella et al. (2010)**
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? 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
Country	Italy
Number of patients	N=1711 with inflammatory bowel disease (Crohn's disease, ulcerative colitis, indeterminate colitis)
Study population	Inclusion: consecutive patients with inflammatory bowel disease who attended at one of 5 university hospitals and 17 general hospitals across Italy as outpatients between January 2002 and December 2004. 860 Crohn's disease (415 females, mean 40 years old range 18-75) 791 ulcerative colitis (371 females, mean 40 years old, range 18-80) 60 indeterminate colitis (27 females, mean 40 years old, range 18-78) One patient with Crohn's disease who has known to have coeliac disease at the time of enrolment was included in the study
Control	n/a
Length of follow-up	n/a
Details of coeliac testing	Clinical charts were reviewed for any risk factors (including anaemia) Serum immunoglobin assays were evaluated to rule out IgA deficiency EMA antibodies with direct immunofluorescence on monkey oesophagus (Bio-Rad, Milan, Italy; positive staining around the smooth muscle was considered positive) TgA antibodies with ELISA (Eurospital, Trieste, Italy; titres above 7 arbitrary units were considered positive) Oesophagogastroduodenoscopy for each patient who was EMA IgA-positive or for patients who were IgA deficient and were assessed according to Marsh classification
Results	**0.5% (9/1711) had serological and histological findings compatible with coeliac disease** - 6 had ulcerative colitis - all had mild to moderate clinical disease activity and all had long-term history of iron deficiency anaemia - 3 had Crohn's – all had moderately active disease (none had iron deficiency anaemia) Both EMA and anti-TgA were positive in 8 but one was positive for EMA and negative for anti-TgA so a conclusive diagnosis of coeliac was not reached for this patient) None had significant signs or symptoms or malabsorption like amenorrhoea, osteoporosis or low albumin or cholesterol levels.

	5 had IgA deficiency but none of these were found to have coeliac disease
Source of funding	Not reported
Conflicts of interest	The paper states that the authors declare that they have no conflicts of interest
Comments	

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

Bibliographic reference	**Leeds et al. (2007)**
Study type	Case control
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	UK
Number of patients	N=354 with IBD, N=173 Crohn's disease N=154 ulcerative colitis N=305 adults with coeliac disease N=601 control
Study population	Inclusion: adult patients registered as having irritable bowel disease in one hospital recruited during attendance at out-patient clinics, N=209 female, median age 45yrs; patients with coeliac disease recruited from the specialist clinic during the annual review, N=222 female, median age 52yrs Those in the coeliac disease group were significantly older than those in the IBD group (p<0.0001) and the control group (p=0.002)
Control	Recruited from 5 general practices in one region
Results	Results of those with coeliac disease who had irritable bowel disease – the prevalence of IBD in coeliac disease 3.3% vs. control 0.33%, OR 9.98 (95%CI, 2.8 to 45.9), p=0.0006

	Coeliac disease in those with irritable bowel disease, N=3/354 (0.85%) vs. N=5/601 with control, OR 1.02 (95% CI, 0.24 to 4.29), p=1.0 NS Stepwise logistical regression was performed to identify factors likely to predict the development of coeliac disease in those with IBD, age, gender, disease type (Crohn's disease or ulcerative colitis) and extent of disease were NS.
Source of funding	Unfunded
Conflicts of interest	
Comments	

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

Bibliographic reference	**Lynch et al. (1995)**
Study type	Cross-sectional data from case control
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	UK
Number of patients	N=22 patients with lymphocytic gastritis
Study population	Inclusion: 22 patients out of 36 patients diagnosed with lymphocytic gastritis between 1984 and 1994 and investigated by upper GI (19 agreed to undergo repeat endoscopy and biopsy; 3 were recently diagnosed resulting in 22 patients included in this study)
Control	The study reports a control group of age and sex-matched controls who were being investigated for dyspeptic symptoms/history but the

	histology results related to coeliac were not reported for the control group
Length of follow-up	Only cross-sectional data
Details of coeliac testing	IgA, IgG and IgM AGA and IgA EMA Biopsy
Results	Apart from the 3 recently diagnosed with lymphocytic gastritis, the results on biopsy for the remaining were: 14 (63.6%) had normal histology 3 (13.6%) had severe villous atrophy 1 (4.5%) had marked villous atrophy
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	The purpose of this study was to investigate the natural history of lymphocytic gastritis and how it related to *H pylori* infection and coeliac disease.

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

Bibliographic reference	**Simondi et al. (2010)**
Study type	Subgroup from 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	N=33 patients with lymphocytic colitis and dyspeptic symptoms

patients	
Study population	Inclusion: patients who were undergoing oesophagogastroduodenoscopy to investigate dyspeptic symptoms from among 80 patients diagnosed with lymphocytic colitis between June 1994 and July 2008 at an outpatient unit of a gastroenterology department (lymphocytic colitis diagnosed if ≥ 20 per 100 surface epithelial cells, subepithelial collagen layer < 10 um, lamina propria with inflammatory infiltration dominated by lymphocytes and plasmacells 28 males; mean age 46.4 years
Control	None
Length of follow-up	n/a
Details of coeliac testing	Anti-EMA and/or tTG with total IgA
Results	4 had Marsh I but not diagnosed with CD
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	Study was primarily about characteristics and investigations in 80 patients with lymphocytic colitis

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

Liver disease

Bibliographic reference	**Bardella et al. (2011)**
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? 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
Country	Italy
Number of patients	N=65 adult patients with primary biliary cirrhosis
Study population	Inclusion: consecutive patients with primary biliary cirrhosis seen during regular follow-up examination Mean age 59 years (range 35-67) 58 women, 7 men
Control	none
Details of coeliac testing	Serum IgA AGA (ELISA, Gluten IgA EIA Pharmacia, Uppsala, Sweden) EMA (indirect immunofluorescence, Eurospital, Trieste, Italy)
Results	0% (no signs of overt malabsorption, no family history of CD, 2 had positive IgA AGA but not EMA and negative biopsy)
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	The study also included the rate of primary biliary cirrhosis in a group of patients with coeliac disease but this was not reproted here as it was not at or before the diagnosis of CD

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

Bibliographic reference	**Chatzicostas et al. (2002)**
Study type	Prospective case series
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	Greece
Number of patients	N=62 adults with primary biliary cirrhosis N=17 adults autoimmune cholangitis
Study population	Inclusion: patients with primary biliary cirrhosis or autoimmune cholangitis Exclusion: biliary obstruction was ruled out with ultrasound, computed tomography and endoscopic retrograde cholangiography No patients had a family history of CD or IgA deficiency Primary biliary cirrhosis: mean age 59 years (range 32-85); 53 women and 9 men Autoimmune cholangitis: mean age 62 years (range 52-77); 16 women and 1 man
Control	100 blood donors were used as controls and 18 patients with CD but these are not extracted here as the blood donors did not receive biopsy and the results from the coeliac patients does not provide a helpful comparison
Details of coeliac testing	From prospectively stored sera over 2 years, the following serological tests were performed: Anti-gliandin (IgA and IgG; ELISA by Alphadia SA/NV, Belgium, values >50 U/ml were considered positive), anti-endomyosial IgA (with monkey oesophagus by Biosystems, Barcelona, Spain and human umbilical cord (Eurospital SpA, Treiste, Italy), anti-reticulin, and IgA class antibodies to guinea pig liver-derived tTG (ELISA kit from QUANTA Lite™ tTG, ELISA, INOVA Diagnostics, San Diego, USA) Small intestinal biopsy was performed if serology was positive
Results	Only 10 of 17 with primary biliary cirrhosis and 5 of 7 with autoimmune cholangitis who had positive serology were given biopsy (4 refused, 5 died shortly after testing positive) **0% had histological features suggestive of CD**
Source of funding	Not reported
Conflicts of interest	Paper reports that there are none
Comments	

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

Bibliographic reference	**Dickey 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	Northern Ireland
Number of patients	N=57 adults with primary biliary cirrhosis
Study population	Inclusion: those attending clinics with primary biliary cirrhosis, N=52 female, mean age 57yrs (30 to 79yrs), none had low total serum IgA
Results	N=6 (11%) EMA +ve, N=4 biopsied all had results consistent with coeliac disease Prevalence of coeliac disease; 1:14 (7%)
Source of funding	Not reported
Conflicts of interest	
Comments	

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

Bibliographic reference	**Drastich et al. (2012)**
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	Czech Republic
Number of patients	N=962 patients with liver diseases
Study population	Inclusion: patients treated in the Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague from 2009 to 2010. <u>Liver diseases:</u> - 152 alcoholic liver cirrhosis - 77 autoimmune hepatitis type I - 117viral hepatitis B - 147 viral hepatitis C - 31 Wilson's disease - 32 primary biliary cirrhosis - 59 primary sclerosing cholangitis - 23 nonalcoholic steatohepatitis - 132 liver steatosis - 14 Budd Chaiari syndrome - 10 polycystic liver - 168 others (drug-induced hepatitis, cryptogenic liver cirrhosis, hepatitis A, hepatocellular carcinoma, focal nodular hyperplasia, mild liver test abnormalities, etc) Mean age 55 years (range 21-76) 378 males, 290 females
Control	The methods of the study reported the use of a control group but results from these patients do not appear to be reported in the paper.
Details of coeliac testing	IgA and IgG anti-tTG (BINDAZYMETM anti-tTG EIA kid, The Binding Site, Birmingham, UK and ORG anti-tTG ELISA kids) Those positive were tested for IgA or IgG (if IgA immunodeficiency) isotypes of anti-AGA and EMA (IgG or IgA [AGA with QUANTA Lite Gliandin IgA or IgG, INOVA Diagnositic Inc, Sandiego, CA, USA and ELISA ANTI GLIANDIN MGP IgA and IgG, The Binding Site; EMA with indirect immunofluorescence with human umbilical cord tissue cryostat sections] Final diagnosis by biopsy
Results	**1.6% (16/962) had biopsy-confirmed CD** (these were 16 of 29 patients who were positive for IgA anti-tTG antibodies who were also seropositive for IgA anti-gliandin and anti-

	EMA) These patients had autoimmune hepatitis type I (n=4), Wilson's disease (n=3), coeliac hepatitis (n=3), primary sclerosing cholangitis (n=2), primary biliary cirrhosis (n=1), Budd-Chiari syndrome (n=1), toxic hepatitis (n=1), non-alcoholic steatohepatitis (n=1)
Source of funding	Czech Ministry of Health, the Academy of Sciences of the Czech Republic, the Czech Science Foundation, Institutional Research Concept Grant
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Eapen et al. (2011)**
Study type	Cross-sectional data from retrospective case control
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	UK
Number of patients	N=30 adults with non-cirrhotic intrahepatic portal hypertension
Study population	Inclusion: patients with non-cirrhotic intrahepatic portal hypertension who were managed in the Liver Unit at Queen Elizabeth Hospital in Birmingham between January 1999 and August 2005; All 5 of the following must be met: portal hypertension (evidenced by any 2 of the following: varicies, hypersplenism, ascites, hepatic venous pressure gradient > 5 mmHg), patent hepatic and portal veins on Doppler ultrasound at diagnosis, no cirrhosis or bridging fibrosis on liver biopsy, exclusion of conditions causing cirrhosis by conventional diagnostic criteria (ie. chronic viral hepatitis, alcoholic hepatitis, etc).

	Exclusion: histological features of another disease process, liver transplantation preceding condition, hepatic malignancy Median age at presentation with non-cirrhotic intrahepatic portal hypertension: 38.5 (IQR 17-74)
Control	There were control groups but these were not relevant for considering coexisting conditions of coeliac disease
Details of coeliac testing	IgA tTG, EMA
Results	16% (5/31) had biopsy-proven CD
Source of funding	One author was supported by a Fellowship award by the European Association for the Study of the Liver for 2004; no further details on funding for the study
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Gatselis et al. (2012)**
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? 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
Country	Greece
Number of patients	N=668 adults with chronic liver diseases
Study population	Inclusion: patients with chronic liver diseases without GI symptoms who attended and were followed up at the Department of Medicine,

	Larissa Medical School, University of Thessaly, Larissa over a 10 year period Liver diseases: - 426 viral hepatitis (275 chronic hepatitis B, 144 chronic hepatitis C, 3 both chronic hepatitis B&C) - 94 autoimmune liver disease (21 autoimmune hepatitis, 45 primary biliary cirrhosis, 24 primary sclerosing cholangitis, 4 with both autoimmune hepatitis and either primary biliary cirrhosis [3] or primary sclerosing cholangitis [1]) - 61 alcoholic disease - 46 non-alcoholic fatty livery disease - 41 other liver disorders (27 undefined hepatic disorders, 3 with benign liver tumours, 1 with Wilson's disease, 1 with transminasemia due to hyperthyroidism, 9 with miscellaneous disorders like mitochondiral disease, benign cholestasis of pregnancy, dysfunction of sphincter of Oddi, a1-antithrypsin deficiency, drug induced hepatitis and secondary hemochromatosis) Median age 53 years (range 26-85) 378 males, 290 females
Control	none
Details of coeliac testing	Anti-DGP IgA, anti-DGP IgG, DGP-IgG and anti-tTG IgA (ELISAs, INOVA diagnostics) Biopsy if positive on serology
Results	29 of 91 who were positive for at least one autoantibody had a biopsy 0.89% (6) had villous flattening on duodenal biopsy and modified Marsh 3a (3 had chronic hepatitis B, 1 had chronic hepatitis B, 1 had alcoholic liver disease, and 1 had undefined liver disease) (Of the others with positive serology and tested with biopsy, 1 had Marsh 1 and the rest had Marsh 0)
Source of funding	Not reported
Conflicts of interest	One author is an employee of INOVA Diagnostics who also supplied some of the ELISA assays (but they did not have an influence on the study design, conduct, or reporting. No other authors received any financial support from any other party.
Comments	

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

Bibliographic reference	**Germenis et al. (2005)**
Study type	Case-control
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
Country	Greece
Number of patients	N=738 N=1350 controls
Study population	Inclusion: consecutive patients with chronic liver disease at an academic liver unit, over the last 5yrs, N=406 males, median age 53yrs (range 6 to 85yrs) (N=462 with viral hepatitis; N=117 with autoimmune hepatitis; N=113 with alcoholic liver disease/non-alcoholic fatty liver disease Total IgA levels in all subjects were within normal limits
Control	
Results	N=4/738 with diverse chronic liver disease IgA EMA +ve; prevalence 1:185 (0.54%) N=3/4 biopsied, N=2 coeliac disease N=4/1350 controls IgA EMA +ve, all biopsied and had histologic changes compatible with coeliac disease; prevalence 1:338 (0.3%)
Source of funding	Not reported
Conflicts of interest	
Comments	

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

Bibliographic reference	**Olsson et al. (1982)**
Study type	Case series
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
Country	Sweden
Number of patients	N=26 patients with primary biliary cirrhosis
Study population	Inclusion: consecutive patients with primary biliary cirrhosis
Control	none
Details of coeliac testing	Biopsy with suction capsule or endoscopic duodenal biopsy Immunoglobin – IgA and IgG
Results	19.2% (5/26) had intestinal villous atrophy (4 had subtotal and 1 had partial) IgA was elevated in 2 and IgG in 3 1 had osteomalacia 1 had diarrhoea of short duration and 1 had no diarrhoea
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	Selection of patients not described

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

Bibliographic reference	**Thevenot T et al. (2007)**
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? 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
Country	France
Number of patients	N=624 adults
Study population	Inclusion: consecutive patients with hepatitis C virus attending 8 outpatients departments between June 2003 and November 2005, N=373 male, mean age 52±14yrs Exclusion: <18yrs, viral hepatitis B infection, +ve HCV antibodies with –ve HCV-RNA
Results	N=1 AEA +ve, biopsy did not show CD, N=34 biopsied in total, none showed CD, prevalence 0%
Source of funding	none
Conflicts of interest	
Comments	

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

Neurological disorders

Bibliographic reference	**Ruggieri et al. (2008)**
Study type	Case control
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

<table>
<tr><td></td><td>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</td></tr>
<tr><td>Country</td><td>Italy</td></tr>
<tr><td>Number of patients</td><td>N=630 children with unknown neurological disorders
N=300 children with known neurological disorders
N=300 healthy controls</td></tr>
<tr><td>Study population</td><td>Inclusion (unknown neurological disorders): consecutive children fully evaluated and found to have neurologic disorders between 1998 and 2004 (90 per year)
- clinical features of patients with unknown neurological disorders: 270 with developmental delay, 180 with epilepsy, 100 with mental retardation, 50 with headache, 12 with chorea, 10 with ataxia and 8 with neuropathy

Inclusion (known neurological disorders): consecutive patients with specific neurological disorders
<table>
<tr><th>Neurological diagnosis</th><th>Number included</th></tr>
<tr><td>Neurofibromatosis type 1 (plus failure to thrive)</td><td>54</td></tr>
<tr><td>Neurofibromatosis type 2</td><td>24</td></tr>
<tr><td>Ruberous sclerosis complex</td><td>42</td></tr>
<tr><td>Complex malformation syndromes (ie. Marfan syndrome, Sotos syndrome, fragile X syndrome, etc)</td><td>23</td></tr>
<tr><td>Brain malformation dysplasia (ie. lissencephaly, cortical heterotopias, double cortex, etc)</td><td>22</td></tr>
<tr><td>Paraneoplastic neurologic syndromes (including leukemia, neuroblastoma, non-Hodgkins lymphoma)</td><td>21</td></tr>
<tr><td>Cerebellar degeneration (including carbohydrate-deficient glycosylation syndromes, episodic ataxia type 2)</td><td>20</td></tr>
<tr><td>Multiple sclerosis</td><td>18</td></tr>
<tr><td>Known leukodystrophies (ie. Krabbe disease, Canavan disease, etc)</td><td>18</td></tr>
<tr><td>Ataxia-telangiectasia</td><td>17</td></tr>
<tr><td>Congenital myasthenia syndromes</td><td>10</td></tr>
<tr><td>Congenital muscular dystrophies (including Fukuyama disease, muscle-eye-brain disease)</td><td>9</td></tr>
</table></td></tr>
<tr><td>Control</td><td>Children matched for age, sex and municipality of residence who attended the Department of Paediatrics for a normal developmental check-up had serological testing</td></tr>
</table>

<table>
<tr><td></td><td>(1.33% [4] had single episodes of febrile seizures and 6% [18] had headache)</td></tr>
<tr><td>Follow-up</td><td>8.7 years (from 4 to 14) in study group with gluten sensitivity</td></tr>
<tr><td>Details of coeliac testing</td><td>IgA and IgG AGA, IgA-class EMA, IgA-class anti-tTG (ELISA method)
Biopsy for all with positive serology (diagnosed based on ESPGHAN criteria)</td></tr>
<tr><td>Results</td><td>Results from biopsy in all groups
<table>
<tr><td>Group</td><td>Positive gut biopsy</td></tr>
<tr><td>Gluten sensitivity (n=835)</td><td>100% (835/835)</td></tr>
<tr><td>Neurologic disorder with unknown cause (n=630)</td><td>1.1% (7)</td></tr>
<tr><td>Neurologic disorder with known cause (n=300)</td><td>0.3% (1)</td></tr>
<tr><td>Healthy controls (n=300)</td><td>0.7% (2)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Conflicts of interest</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Study also reports the rate of neurological disorders in a group of patients with gluten sensitivity but this was not presented here as it was not compared to the rate of neurolgoical disorders in a control group</td></tr>
</table>

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

Sarcoidosis

Bibliographic reference	**Papadopoulos et al. (1999)**
Study type	Cross-sectional survey with historical control
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=78 with sarcoidosis
Study population	Inclusion: patients with documented sarcoidosis attending the Department of Medicine between January 1990 and December 1991 Of 89 patients, 6 could not be located, 1 was deceased and four refused to participate in the study 34 females/44 males Median 48 years (range 22-81) Median observation since diagnosis of sarcoidosis: 120 months (range 1-468) Histological diagnosis of sarcoidosis was present in 66% (51/78) 35.9% (28/78) had received corticosteroids
Control	Data from a previously published study of healthy blood donors using the same serological detection methods(no other details including numbers of patients are reported)
Details of coeliac testing	AGA – IgA/IgG in all patients (ELISA) Those positive were offered a biopsy
Results	Of 12 with elevated AGA titres, 11 were offered small biopsy (1 had been previously diagnosed) but 8 agreed. Apart from the one patient with histologically diagnosed CD before the study, all 8 biopsies were normal without villous atrophy or increased IELs (**0% CD-confirmed biopsy during the study**) **1.3% (1/78) if previously-diagnosed CD is included compared with 0.065 in the control group (p=0.09)**
Source of funding	Nordisk Insulin Foundation Committee, the Albert Påhlsson Foundation, the Ernhold Lundström Foundation, Malmö Sjukvårdsförvaltning, University of Lund, and Alfred Österlund Foundation
Conflicts of interest	Not reported
Comments	

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

Sjogren syndrome

Bibliographic reference	**Szodoray et al. (2004)**
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? 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
Country	Hungary
Number of patients	N=111 adults with Sjögren Syndrome
Study population	Inclusion: consecutive patients with Sjögren Syndrome attending an outpatient clinic
Details of coeliac testing	
Results	N=5/111 (4.54%) diagnosed with CD The age of those with CD 39.8 (28 to 53) vs. those without CD 57 (38 to 77), p<0.001 Duration of Sjögren syndrome at the time of the study similar in both groups GI symptoms, N=41/111 (36.93%) abdominal discomfort, N=11 (7.2%) lack of appetite, N=6 (5.4%) nausea, N=10 (9%) diarrhoea, N=6(5.4%) iron deficiency anaemia due to malabsorbtion
Source of funding	Grants from the National Research Fund and the Ministry of Welfare
Conflicts of interest	
Comments	

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

Systemic sclerosis

Bibliographic reference	**Forbess et al. (2004)**
Study type	Cross section data from a large case series
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=72 patients with systemic sclerosis
Study population	Inclusion: patients participating in the Scleroderma Registry at the Hospital for Special Surgery enrolled from August 2006 to April 2011 with a clinical diagnosis of diffuse or limited systemic sclerosis and an available serum sample; sample size was restricted from 103 to 72 due to limited funding for the study and cost of the arrays Exclusion: localised scleroderma or evidence of overlap with another connective tissue disease Mean age: 51 (SD 13) 88% female 54% diffuse 46% limited disease Mean duration of diagnosis (from onset of first non-Raynaud's symptom): 6 (SD 7) 84% had joint involvement ~50% had sicca symptoms 88% had GI involvement

Details of coeliac testing	Stored sera were tested for anti-tTG IgA and IgG and anti-DGP IgA and IgG (ELISA assay kits from INOVA, San Diego, CA, USA) If any were positive, anti-EMA were tested (Quest Diagnostics, NJ, USA) Bowel endoscopy and biopsy for any positive on serology
Results	3 were positive on serology (one on anti-tTG and two on anti-DGP IgA antibodies) (none for antiEMA) 2 of these 3 patients had biopsy as one died 0% (0/72) had biopsy-confirmed CD (both with positive serology had Marsh 0)
Source of funding	Clinical and Translational Science Centre at Weill Cornell Medical Centre Clinical and the Rudolf Rupert Scleroderma Program at the Hospital for Special Surgery (also, one of the authors received funding from the Scleroderma Foundation New Investigator Grant)
Conflicts of interest	The authors declared no conflicts
Comments	

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

Autoimmune thyroid disease

Bibliographic reference	**Saatar et al. (2011)**
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=302 patients with autoimmune thyroid disease
Study population	Inclusion: patients (adults and children) with positive anti-thyroid antibodies who were recruited from a paediatric endocrinology service

	at a hospital; criteria included positive thyroid peroxidase antibodies, positive thyroglobin antibodies or positive thyroid stimulationg hormone receptor antibodies Exclusion: congenital hypothyroidism, negative thyroid antibodies, IgA deficiency 287 of 668 patients consented but 71 dropped out before study completing and 13 were excluded because of negative antibodies and 1 because of IgA deficiency, leaving 302 patients remaining Age from 3.1 to 24.9 years (most were 17 years old or less) 238 female, 64 male 24 had comorbidities (13 with T1DM, 10 with Down's syndrome, 2 with Turner syndrome; 1 had both T1DM and Down's syndrome)
Control	none
Details of coeliac testing	Total IgA tTG-IgA Biopsy if positive tTG-IgA
Results	**2.4% (7/302) had biopsy-confirmed CD** 4.6% (14/278) had positive serology (13 had biopsy but one did not consent to biopsy) Excluding those with comorbidities, the prevalence of CD was 1.3% which authors say is similar to the rate in the general population
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Sategna-Guidetti C et al. (1998)**
Study type	Case control
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=152 autoimmune thyroid diseases N=185 with coeliac disease N=170 control
Study population	Inclusion: consecutive patients at a thyroid outpatients clinic none of who were taking medications that could interfere with the immunological response, N=100 with Graves' disease, N=52 autoimmune throiditis/ subclinical hypothyroidism/euthyroidism, N=128 female, ages 15 to 80yrs Consecutive patients attending a coeliac disease outpatients, N=53 (N=41 female, median age 36yrs, range 19 to 67yrs) newly diagnosed therefore untreated, N=132 (N=89 female, median age 37yrs, range 16 to 81yrs)on GFD
Control	healthy volunteers
Details of coeliac testing	
Results	**EMA and biopsy +ve N=5/152 (3.29%) of those with autoimmune thyroid diseases** Autoimmune thyroid disease identified in N=38/185 (20.54%) of those with coeliac disease vs. N=19/170 control group (11.17%), X2 =5.09, p=0.02, the prevalence of autoimmune thyroid diseases among patients and controls did not differ among age groups
Source of funding	Not reported
Conflicts of interest	
Comments	

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

Bibliographic reference	**Spadaccino 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=271 patients with autoimmune thyroid disease
Study population	Inclusion: patients with autoimmune thyroid disease (181 chronic thyroiditis, 90 with Graves' disease) 5 patients with chronic thyroiditis already had known CD and were on a GFD so were not included here Patient characteristics below include the 5 patients who already had known CD and were on a GFD (otherwise, these patients were not included in this evidence table) Mean age 42.6 years (range 12-89); 269 adults and 7 children 246 females, 41 males 141 had 2 or more clinical autoimmune diseases and depicted autoimmune polyglandular syndromes
Control	none
Details of coeliac testing	IgA-tTGA (ELISA, QUANTA Lite, Inova Diagnostics Inc., San Diego, USA; < 20 U were considered normal) All were tested for IgA levels IgG AGA (ELISA, Giandin IgG, QUANTA) EMA-IgA using indirect immunofluorescence Biopsy – graded with Marsh criteria
Results	**1.8% (5/276) had biopsy confirmed CD** - 4 had chronic thyroiditis - 1 had Graves' disease (10 patients were positive for coeliac –related antibodies)
Source of funding	Not reported
Conflicts of interest	Not reported

Comments	

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

Turner syndrome

Bibliographic reference	**Bonamico et al. (2002)**
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=389
Study population	Inclusion: patients with Turner syndrome enrolled by the Italian Society of Pediatric Gastroenterology and Hepatology and the TS Italian Study Group from various centres of the northern, central, southern, and insular regions, making the sample fairly representative of the whole population, age range 7 to 38yrs
Details of coeliac testing	IgA AGA and/or EMA and biopsies
Results	N=25 (6.4%) diagnosed with coeliac disease N=10 (40%) classic form of coeliac disease, N=8 (32%) atypical, N=7 (28%) silent
Source of funding	Consiglio Nazionale delle Ricerche Grant
Conflicts of interest	
Comments	

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

Bibliographic reference	**Dias et al. (2010)**
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=56 women with Turner Syndrome
Study population	Inclusion: women with Turner syndrome confirmed on cytogenetic testing who were followed at a Clinical Genetic Unit a t a hospital and who were on a gluten-containing diet and without a prior diagnosis of CD Mean age at diagnosis: 5.5 ± 4.4 years Mean age at CD screening: 17.0 ± 9.3 years (from 10 month to 52 years)
Control	none
Length of follow-up	n/a
Details of coeliac testing	IgA levels (<5 mg/dL were considered abnormal) IgA EMA (distal portion of monkey oesophagus used as antigenic substrate, Inova Diagnostics, and fluorescein-labelled goat antibody as second substrate); confirmation with ELISA, Inova Diagnostics Biopsy if positive serology (characterised with Marsh criteria)
Results	3.6% (2/56) had biopsy-confirmed CD (both had positive IgA-EMA and IgA-tTG)
Source of funding	Celiac disease Investigation laboratory, Department of Paediatrics, University of Brasilia School of Mediciine, Brasilia

Conflicts of interest	Paper reports no conflicts of interest concerning this research
Comments	

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

Bibliographic reference	**Frost et al. (2009)**
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? 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
Country	UK
Number of patients	N=256 women with Turner Syndrome
Study population	Inclusion: consecutive women with karyotypically proven Turner syndrome attending an Adults Turner clinic as part of a health surveillance programme Median 29 years old (range 16 to 61)
Control	none
Length of follow-up	n/a
Details of coeliac testing	EMA using indirect immunofluorescence analysis with commercially available fixed sections of monkey oesophagus (Biodiagnostics Ltd, Worcestershire UK) as antigen substrate; diluted to 1:10) EMA IgA was detected with FITC-labelled sheep anti-human IgA conjugate (Dako, Ltd, Ely, UK) All positive patients were offered duodenal biopsy

	HLA typing was also offered to patients with positive EMA serology or previous diagnosis of CD
Results	5 were diagnosed prior to transition to adult care following clinical presentation Of the 251 without pre-diagnosis of CD, **3.2% (8/251) were positive for EMA** (none had symptoms suggestive of CD) All but one patient who denied biopsy were tested for histological signs of CD: **Partial or total villous atrophy was present in 2.8% (7/251)**
Source of funding	No specific grants for this research were received (however, the work was undertaken at UCLH/UCL who received a proportion of funding from the DH's NIHR Biomedical Research Centres funding scheme
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Mortensen et al. (2009)**
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	Denmark
Number of patients	N=107 patients with Turner syndrome
Study population	Inclusion: Danish Turner syndrome patients from the National Society of Turner Contact Groups in Denmark (through advertisement), and a number of hospital; all had undergone chromosome analysis

	Median age 36.7 years (range 6 -60)
Control	None
Length of follow-up	n/a
Details of coeliac testing	Total IgA was measured IgA AGA and IgA anti-tTG If IgA deficiency, AGA and anti-tTG IgG were determined
Results	**Anti-tTG, AGA or both were present: 18% (19/106)** **In 2 CD was known previously and 3 received a CD diagnosis (overall prevalence of diagnosed CD: 4.7% [5/106])** 97% (103/106) had normal IgA serum range The four youngest patients did not have autoantibodies Those with positive antibodies (for any autoimmunity) were significantly older than those without (38.0 ± 13.5 vs 29.4 ± 13.0 years, p = 0.001)
Source of funding	Dronning Louise Børnehospitals Forskningsfond
Conflicts of interest	Paper reports that the authors declared no conflicts of interest
Comments	Study considered prevalence of a number of autoimmunities in Turner syndrome, but only those related to coeliac disease are presented here

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

Type 1 diabetes

Bibliographic reference	**Adlercreutz., EH. (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? 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
Patient characteristics	N = 662 Swedish children with T1D; 1080 Danish children with T1D; 309 healthy children from Sweden; 283 healthy Danish children. All children were diagnosed with T1D between 1995 and 2006. Samples were collected at the time of diagnosis. Healthy controls were recruited from local schools in both Denmark and Sweden. Swedish T1D: • N=662 • 305 = female • Median age = 10.2 (1 - 17.9) Danish T1D • N=1080 • Female = 518 • Median age = 10.3 (0.6 - 17.8)
Comorbid condition	Type 1 diabetes (T1D)
Investigations	Serological testing • Conjugated IgA/IgG DGP tTG • IgG tTG Celiac disease autoimmunity was defined as being positive for both IgA/G DGP tTG and IgG tTG HLA genotyping • HLA DQ genotyping
Results	Swedish T1D • Prevalence of CD = 17.2% (114/662) Danish T1D • Prevalence of CD = 11.7% (126/1080)
Funding	None listed
Other comments	NO Biopsy confirmed diagnosis of CD

Bibliographic reference	**Barbato et al. (1998)**
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? 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
Country	Italy
Number of patients	N=175 patients with insulin dependent diabetes
Study population	Inclusion: Patients with insulin dependent diabetes mellitus (no further inclusion criteria provided) 51.4% male Age from 1 to 30 years (102 were paediatric [between 6 and 14 years] and 73 were adults)
Control	none
Length of follow-up	n/a
Details of coeliac testing	IgA and IgG AGA (using fluorescent immunoenzymatic test, Eurospital) Anti-endomysium antibodies (AEA) (using indirect immuno-fluorescence with those who fluoresced only in reticular tissues as positive, Medic) anti-reticulin antibodies (ARA) (using indirect immuno-fluorescence with those who fluoresced only in reticular tissues as positive, Eurospital) If tests positive for AEA (with or without positivity for ARA and AGA), intestinal biopsy was performed
Results	Overall seroprevalence: 25.6% (45/175) Anti-endomysium antibodies (AEA) – 21 had pathological values

	23 had biopsy (21 with pathological values for AEA and 2 with pathological values for only ARA) – all 21 with pathological values for AEA had villous atrophy Prevalence of CD in children with diabetes: 8.8% (9/102; 95% CI 3.3 to 14.3) Prevalence of CD in adults with diabetes: 16.4% (12/73; 95% CI 7.9 to 24.9) Presenting symptoms at diagnosis included diarrhoea and weight loss in 2 (16 and 17 years old) and others had one or more of growth failure in height and/or weight, recurrent abdominal pain, abdominal distension, lack of appetite, mood changes, headache, sideropenic anaemia. (all symptoms disappeared after GFD was introduced)
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Cev et al. (2010)**
Study type	Cross-sectional data from case series
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	Romania
Number of patients	N=307 patients with T1D

Study population	Inclusion: patients with T1D prospectively enrolled from January 2004 to December 2008 who had presented at a centre for evaluation and rehabilitation for children and adolescents 158 females, 149 males Median age 27 years (range 14-38)
Control	None
Length of follow-up	n/a
Details of coeliac testing	tTGA (IgA and IgG) (ELISA with human recombinant tTG as antigen with Test ESKULISA, CeliCheck, Germany; values greater than 24 U/ml were considered positive) If positive, IgA EMA (indirect immunofluorescence using unfixed cryosections of monkey oesophagus) If positive on tTGA, duodenal biopsy assessed with Marsh system
Results	5.5% (17) with positive tTGA 16 has biopsy 3.9% (12) with biopsy-confirmed CD - four Marsh 0 (not considered CD) - 2 Marsh 1 - 1 Marsh 2 - 9 Marsh 3
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	Study also reports results after treatment on GFD but this was not extracted here

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

Bibliographic reference	**Djurić et al. (2010)**
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	Serbia
Number of patients	N=121 children and adolescents with T1D N=125 healthy children and adolescents as control
Study population	Inclusion: children and adolescent with T1D who were admitted to a university hospital or observed on an outpatient basis from October 2004 to December 2007 70 girls, 51 boys Mean age 10.4 years
Control	Healthy children and adolescents identified as healthy from their medical records and routine physical examinations from south east Serbia
Length of follow-up	n/a
Details of coeliac testing	Serum IgA Anti-tTG IgA (ELISA, Euroimmun; 20 RU/ml was cut-off) / anti-tTG IgG (ELISA) if IgA deficient Biopsy if serologically positive (ESPGHAN criteria)
Results	9 (7.4%) were serologically positive on tTG IgA Of 4 with selective IgA deficiency, all had negative IgG tTG Biopsy-proven CD: 5.79%(7) vs 0.8% (1) ($p < 0.05$) (T1D group: 2 had Marsh IIIa, 3 had Marsh IIIb, 2 had Marsh IIIc; the positive control participant had Marsh IIIa)
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	

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

Bibliographic reference	**Galván 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	Cuba
Number of patients	N=208 patients with T1D
Study population	Inclusion: patients with T1D who were diagnosed as positive for antibodies against islet cells and/or glutamic acid decarboxylase isoform 65 (antibodies against GAD65) requiring insulin treatment at diagnosis Mean 19 years old (range 2-58) 116 male, 92 female
Control	none
Length of follow-up	n/a
Details of coeliac testing	tTGA IgA (immunochromatographic test, HeberFast Line® anti-transglutaminase and also ELISA) Biopsy if positive tTGA
Results	14 patients were positive on both arrays (2 had symptoms) 6 agreed to biopsy (including the 2 with symptoms) and had features consistent with CD with 2.88% (6/208) biopsy-confirmed prevalence: - 5 had partial villous atrophy with elevated IEL counts - 1 had subtotal villous atrophy - (mean age at diagnosis: 11.00 ±4.56 years
Source of funding	Not reported
Conflicts of interest	Not reported

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

Bibliographic reference	**Kakleas et al. (2010)**
Study type	Comparative 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	Greece
Number of patients	N=105 children and adolescents with type 1 diabetes mellitus
Study population	Inclusion: children and adolescents with T1DM regularly followed at the Diabetic Clinic of the Second University Department of Paediatrics between 2005 and 2007 Mean ± SD: Age: 12.44 ± 4.76 years Duration of diabetes: 4.41 ±3.70 Age at diabetes diagnosis: 8.01 ± 3.17 years 50.4% male HbA1c levels: 8.13 ± 1.70%
Control	Study compared those with and without tTG IgA seropositivity for CD
Length of follow-up	n/a
Details of coeliac	Anti-tTG IgA class antibodies were detected by ELISA (using DYNEX DSX ELISA analyser; human native tissues transglutaminase

testing	from red blood cells was used; 20-30 units was considered to be weakly positive [Inova Diagnostics, USA]) If high values of tTG IgA was discovered on 2 consecutive measurements (60 units or more), jejunal biopsy was performed Conclusive diagnosis on typical mucosal findings including lymphocytic infiltration, hypertrophy of the crypts and villous atrophy(Marsh II) Serum total IgA levels were determined to detect IgA deficiency
Results	Serological results: **Anti-tTG IgA positivity: 8.6% (9/105)** (only 5 had mild intestinal symptoms, iron deficiency anaemia and growth retardation) No differences between males/females, BMIHbA1c levels, but patients with positive anti-tTG IgA were significant younger (p=0.038), had shorter T1DM duration (p=0.056) and shorter height (p=0.055) Univariate regression analyses showed that the likelihood of anti-tTG IgA positivity was: - approximately 18% greater [95% CI 0.68-0.99) in younger patients with T1DM - 30% greater in those with short T1DM duration [95% CI: 0.48, 1.04]) Multivariate logistic regression indicated that the patients' present age was the only determinant associated with anti-tTG IgA positivity: younger children with T1DM had 22% more odds of presenting with anti-tTG IgA positivity (OR:1.22, 95% CI 1.01-1.45) Biopsy results: **5 patients (4.8%) had biopsy-proven CD** (the same 5 were those who had symptoms and anti-tTG IgA positivity with high titres 60 or more units)
Source of funding	Not reported
Conflicts of interest	Study reports that there are none
Comments	

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

Bibliographic reference	**Leeds et al. (2010)**
Study type	Cross-sectional data (for prevalence) and case-control
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

<table>
<tr><td></td><td>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</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Number of patients</td><td>For cross-sectional data: N=1000 with T1D; N=1200 healthy controls
For case-control: N=12 with newly diagnosed CD and T1D, N=24 matched controls with T1D but not CD</td></tr>
<tr><td>Study population</td><td>Inclusion: patients with T1D aged >16 years
Exclusion: patients < 16 years, inability to consent , diabetes other than type 1

43 patients refused to participate, resulting in 1000 included overall
Mean age 43.2 years
439 females
21 patients already had established CD and T1D and were included in the analyses</td></tr>
<tr><td>Control</td><td>For cross-sectional data: screening of 1200 healthy volunteers from 5 separate general practices in Sheffield
For case-control: 2 control subjects with T1D, matched for every case by age, sex, weight, and diabetes duration</td></tr>
<tr><td>Length of follow-up</td><td>Not reported here</td></tr>
<tr><td>Details of coeliac testing</td><td>IgA EMA, IgA anti-tTG and total IgA
All with either positive antibody or low IgA level were offered a duodenal biopsy; histological features consistent with CD were classified according to Marsh staging with grade 3 changes(villous atrophy) considered diagnostic for CD</td></tr>
<tr><td>Results</td><td>Prevalence of CD:
<table>
<tr><td></td><td>Newly diagnosed</td><td>Including the 21 who already had established CD</td><td>Control group</td><td>Comparison of all CD patients with control group</td></tr>
<tr><td>Prevalence of CD</td><td>12% (12/1000)*</td><td>3.3% (33/1000; 95%CI 2.3-4.6)</td><td>1% (12/1200; 95%CI 0.5-1.7)</td><td>OR 3.3 (95%CI 1.7-6.6, p< 0.0001)</td></tr>
</table>
*6 had GI symptoms, 1 was anaemic, 2 were negative for EMA) – 12% undetected CD

4 patients with positive antibodies refused to be tested. Authors calculated that if all had biopsy-proven CD, the prevalence would be 3.7% (37/1000; 95%CI 2.6-5.1)

21 patients tested positive for EMA but did not have biopsy considered CD so were considered to have potential CD – 18 of these had completely normal biopsies but 3 had increased IELs; these patients were not included in the overall rate of CD and were excluded from</td></tr>
</table>

	investigations in this study A comparison between those with T1D and newly diagnosed CD and matched controls showed that patients were well matched but that those with CD and T1D had significantly higher HbA1C (median 8.2% vs 7.5%, p=0.05), significantly lower cholesterol (median 4.1 vs 4.9 mmol/L, p=0.014), and significantly lower HDL (median 1.1 vs 1.56 mmol/L, p=0.017). These patients also had a significantly higher proportion with nephrology stage > 3 (41.6% vs 4.2%) and advanced retinopathy (58.3% vs 25%). However, there was no difference in quality of life, cholesterol-toHDL ratio, triglycerides, eGFR, or proportion with peripheral neuropathy. Of those with newly identified CD, 3/12 had abnormal bone density (on DEXA scan) and 16.7% (2/12) were considered as having osteoporosis and 8.3% (1/12) considered as having osteopenia.
Source of funding	Bardhan Research and Education Trust of Rotherham and Solvay
Conflicts of interest	Paper reports no potential conflicts relevant to the article
Comments	This is data from a larger study considering the prevalence of microvascualr complications in adults with T1D and newly diagnosed CD; data was available after 1 year but as this included patients on a GFD, this data was not extracted here.

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

Bibliographic reference	**Pham-Short et al. (2010)**
Study type	Case series
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	Australia
Number of	N=4379 young people with T1D

<table>
<tr><td>patients</td><td></td></tr>
<tr><td>Study population</td><td>Inclusion: people aged 18 years or younger with T1D attending a tertiary diabetes centre in New South Wales between January1990 and December 2009

49% (2147) male
Mean age at diabetes diagnosis was 6.6 ± 4.0 compared with 8.4 ± 4.1 in those without CD (P< 0.001)</td></tr>
<tr><td>Control</td><td>None</td></tr>
<tr><td>Length of follow-up</td><td>Study conducted over a 20-year period</td></tr>
<tr><td>Details of coeliac testing</td><td>Screening for coeliac disease at diagnosis and 1-2yearly using anti-EMA IgA and/or anti tTG IgA antibodies
(EMA used until June 2004 with indirect immunofluorescence and anti-tTG IgA after June 2004 with enzyme-linked immunosorbent assay)
CD diagnosed with small bowel biopsy based on Marsh scores III or greater</td></tr>
<tr><td>Results</td><td>4.2% (185/4379) were diagnosed with coeliac disease (45% within 2 years, 78% within 5 years, and 94% within 10 years of diabetes diagnosis)
Of these 33% (61) were EMA or anti tTG IgA positive at diagnosis of diabetes

Incidence of coeliac disease:
<table>
<tr><td>Time period</td><td>Incidence of CD (95% CI)</td></tr>
<tr><td>Over entire 20 year period</td><td>7.7 per 1000 person years (6.6-8.9)</td></tr>
<tr><td>1990-1999</td><td>7.5 per 1000 person years (5.8-9.5)</td></tr>
<tr><td>2000-2009</td><td>7.7 per 1000 person years (6.4-9.3)</td></tr>
</table>
(difference between the 2 decades was not significant)

In 2009, the prevalence of CD was 7.1% (95% CI 5.6-8.8) (75 were biopsy-proven over 1051 clinic population)

Comparison of age at diagnosis of diabetes:
<table>
<tr><td rowspan="2"></td><td colspan="3">Age at diabetes diagnosis</td><td rowspan="2">p value*</td></tr>
<tr><td>< 5 years (n=80)</td><td>5-10 years (n=61)</td><td>≥10 years (n=44)</td></tr>
<tr><td>Mean age at CD diagnosis (SD)</td><td>7.1 (3.4)</td><td>10.5 (2.6)</td><td>13.3 (1.6)</td><td>Not reported</td></tr>
<tr><td>Male gender</td><td>50%</td><td>46%</td><td>51%</td><td>NS</td></tr>
<tr><td>Median time in years to diagnosis of CD after diabetes diagnosis (range)</td><td>3.0 (0.1-14.3)</td><td>2.1 (0.1-10)</td><td>0.7 (0.2-3.8)</td><td>< 0.001</td></tr>
<tr><td>Diagnosed with CD within</td><td>33%</td><td>48%</td><td>75%</td><td><0.01</td></tr>
</table>
</td></tr>
</table>

	2 years of diabetes				
	Incidence of CD per 100 person years (95%CI)	10.4 (8.2-13.0)	6.5 (4.7-8.8)	6.4 (4.9-8.2)	<0.01
	* <5 years compared to ≥10 years				
Source of funding	Not reported				
Conflicts of interest	Authors state that there is nothing to declare				
Comments					

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

Bibliographic reference	**Picarelli et al. (2005)**
Study type	Case control
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
Country	Italy
Number of patients	N=94 adults with insulin-dependent diabetes mellitus 1 N=83 control
Study population	Inclusion: consecutive adult patients with IDDM1 regularly attending a centre for the study of diabetes, N=43 male, N=51 female, mean age 46.9yrs (range 18 to 70yrs), none had any symptoms attributable to enteropathy, any evidence of malabsorbtion or been previously diagnosed with coeliac disease, all on gluten containing diet
Control	blood donors without IDDM1, CD, other auto-immune conditions, or first-degree relative with any autoimmune condition

Details of coeliac testing	
Results	All had IDDM1 for >15yrs and satisfactory metabolic control N=13 (6.4%) with coeliac disease EMA =ve vs. EMA –ve
Source of funding	Ministry of University and Research (MIUR), the non-governmental association for research on coeliac disease and diabetes mellitus
Conflicts of interest	
Comments	

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

Bibliographic reference	**Salardi et al. (2008)**
Study type	Case series (retrospective and prospective)
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? YERS (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
Country	Italy
Number of patients	N=331 children with type I diabetes
Study population	Consecutive children newly diagnosed with type I diabetes mellitus in a paediatric clinic between 1987 and 2004 (sera was stored between 1987 and 1993 and this was retrospectively tested for CD-related antibodies) Mean age: 8.1 ± 4.3 years (range 0.08-14.9)

Control	None
Length of follow-up	Immunological evaluation at diagnosis of diabetes, every 6 to 12mths after (duration 1 to 18yrs, mean 9yrs)
Details of coeliac testing	IgA EMA (indirect immunuofluorescence using monkey oesophagus commercial kits, Eurospital, Trieste, Italy) and human umbilical cord cryostat sections (were tested to the dilution of 1:5 and were titrated to the end point if positive) Diagnosis was confirmed by intestinal biopsy with gastroduodenoscopy and multiple biopsies with specimens graded according to Marsh classification
Results	Apart from 2/331 patients who were diagnosed with CD before they were diagnosed with diabetes, 29 additional patients had positive EMA assay – 6 did not have biopsy as they had borderline EMA positivity (n=2) or because EMA became negative without a GFD (n=4). 23 patients had biopsy – 18 had typical CD lesions and 5 had normal mucosa; however, 2 of these 5 had a second biopsy at 1 and 4.5 years after the onset of symptoms showing typical CD lesions 6.0% (20/331) had biopsy-proven CD (an additional 2 patients had been diagnosed with CD before being diagnosed with diabetes and were on a GFD) (After 1994, the prevalence was 10.6% [16/151] and before 1994 it was 3.3% [6/180] [p=0.015])
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	(author's comment: same screening methods (EMA), all tests carried out in the same reference lab, consistent assay performance, population referring to the clinic did not change over time, suggest that the risk of CD increased in diabetic children after 1994)

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

Bibliographic reference	**Smith et al. (2000)**
Study type	Cross-sectional data (for prevalence) from case series
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 – (unselected population) 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
Country	Australia
Number of patients	N=281 children and adolescents with T1D
Study population	Inclusion: children and adolescents with diabetes mellitus attending a paediatric diabetes clinic between January 1993 and December 1998 Mean and SD: Age 9.9 ± 3.8 years (range 1.3 to 18 years) 133 females/136 males One patient had prior diagnosis of CD before onset of diabetes
Control	None
Length of follow-up	Only cross-sectional data extracted
Details of coeliac testing	AGA-IgG and AGA-IgA If positive AGA-IgG and undetectable AGA-IgA, total serum was measured to exclude IgA deficiency Those with double positive AGAs had gastro-duodenoscopy and multiple biopsy to confirm CD according to ESPGAN criteria CD diagnosis was based on increased IELs, crypt hyperplasia and/or increase in inflammatory cells in the lamina propria in addition to either total or partial villous atrophy
Results	Double positive AGAs: 12.5% (35/280) None had IgA deficiency **Overall CD prevalence: 5.7% (16/281)** (with initial biopsies confirming CD diagnosis; this rate includes the one patient with previously diagnosed CD) Of those diagnosed on biopsy, 7 had gluten challenge and third a biopsy under ESPGHAN criteria to confirm the diagnosis, and 4 have completed 2 biopsies; one declined a gluten challenge after the initial biopsy due to extreme gluten sensitivity and four had yet to complete a confirmatory biopsy on a GFD and/or gluten challenge at the writing of the paper) 5 with double positive antibodies did not have biopsy: one because of loss to follow-up and 4 declined because they were asymptomatic
Source of funding	Not reported
Conflicts of interest	Not reported
Comments	The purpose of the study was to look at the prevalence of CD in diabetese mellitus and also consider the longitudinal changes in AGA status – only the cross-sectional data on prevalence was included here.

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

Bibliographic reference	**Uibo et al. (2010)**
Study type	Cross-sectional survey and prospective case series of some patients
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	Estonia
Number of patients	N=271 children with type 1 diabetes
Study population	Inclusion: T1D patients from 2 main children's hospitals in Estonia who were investigated between 1995 and 2006 (T1D definition made according to the WHO and International Society for Paediatric Adolescent Diabetes criteria) For cross-sectional data/initial screening study (n=271): 57% male Mean age: 10.6 years (range 1.7-18.0) Mean age at diagnosis of T1D: 8.3 years (range 1.6-17.7) N=122 at diagnosis of T1D N=149 after diagnosis of T1D (0.1 to 14.8 years after diagnosis) For prospective case series: N=73 of the 271 patients included in the initial screening study (56.2% male, age range: 1.7-16.2)
Control	none
Length of follow-	n/a for cross-sectional data Not reported for case series

up

Details of coeliac testing

IgA EMA and IgA tTGA (until 2000, only EMA; in 2003 all who had been tested so far were re-tested with tTGA)
(IgA levels were tested to rule out IgA deficiency with DPS Immulite assay)
Those with antibodies and/or with coeliac-disease related symptoms were invited for small intestinal biopsy
Diagnosis of CD according to criteria recommended by ESPGHAN

Results

Results of testing:

	Initial screening/cross-sectional survey (n=271)			Prospective follow-up (n=73)		
	Rate with/without symptoms (95% CI)[1]	tTGA/EMA results	Biopsy results[4]	Those who continued in prospective study	tTGA/EMA results	Biopsy results
With symptoms	2.2% (6/271; 95% CI 0.90-4.99)	5/6 negative	Marsh 0-5[2]	0	n/a	n/a
		1/6 positive	n/a (refused)	1	Negative	n/a
Without symptoms	265/271	254 negative	NA	73	71 negative 2 positive	n/a MIIIa&IIIb[3]
		11 positive	1 M0 1 MIIIa[3] 1MIIIb[3] 1 n/a (refused)	0	n/a	n/a

[1] not a statistically significant difference, [2] authors considered this to be normal mucosa, [3] considered to be coeliac disease, [4] rate of those with biopsy-proven CD was considered statically significant than the EMA/tTG negative group ($p<0.01$)

(none had IgA deficiency)

Rate of CD:

	Rate (95% CI)	Patient characteristics of those diagnosed	Presence of symptoms in those diagnosed
Primary screening (n=271)	3.3% (9/271; 95% CI 1.63-6.42)*	Mean age 9.9 years (3.1-16.2)	None
Prospective case series (n=73)	2.7% (2/73; 95% CI 0-0.072)	Both 10 years with duration of T1D 3.2 and 3.3 years	None
Overall in 1995-2006	4.1% (11/271)	7 girls, 4 boys	None

* CD was diagnosed simultaneously with T1D in 2 patients but mean 3.4 years (range 0.9-6.9) after the T1D diagnosis in the other 7.

Source of funding

Estonian Science Foundation and Estonian Ministry of Education and research

Conflicts of

Not reported

interest	
Comments	

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

Abbreviations

ACR – American College of Rheumatology

CD – coeliac disease

CI – confidence interval

DMARDs – disease-modifying anti-rheumatic drug

EATL – enteropathy-associated T-cell lymphoma

ELISA – enzyme-linked immunosorbent assay

EMA – anti-endomysial antibodies

FSH – follicle-stimulating hormone

GI - gastrointestinal

GFD – gluten-free diet

GORD – gastro-oesophageal reflux disease

HR – hazard ratio

IBD – inflammatory bowel disease

IBS – irritable bowel syndrome

IDDM1 – insulin-dependent diabetes mellitus 1

IELs – intraepithelial lymphocytes

IQR – intraquartile range

IRR – incidence rate ratio

LH - luteinizing hormone

NIH – National Institute of Health (USA)

SD – standard deviation

SIR – standardised incidence ratio (ratio of the observed to the expected cases)

SMR – standardised mortality rate

T1D/T1DM – type 1 diabetes / type 1 diabetes mellitus

TCR – T-cell receptor

anti-tTG – anti-transglutaminase antibodies

UJ – ulcerative jejunitis

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

Abbreviations

CD – coeliac disease

EATL – enteropathy-associated T-cell lymphoma

EMA – anti-endomysial antibodies

GI – gastro-intestinal

GFD – gluten-free diet

GORD – gastro-oesophageal reflux disease

HLA-DQ2/ HLA-DQ8 – human leukocyte antigen serotypes

IEL – intraepithelial T-lymphocyte

IQR – intraquartile range

NR – not reported

NS – not significant

TCR – T-cell receptor

UJ – ulcerative jejunitis

D.3 Review question 4.3

Evidence table – Canavan et al. (2011)

Study type	Non-randomised comparative case series
Country	UK
Number of patients	N=7527 adults with undetected CD
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes - roughly 16 years 7. What are the results? Undetected CD in adults over the age of 45 does not confer increased mortality risk 8. How precise are the results? Precise but cross line no effect 9. Do you believe the results? Yes 10. Can the results be applied to the local population? Yes 11. Do the results fit with other available evidence? Yes 12. What are the implications of this study for practice? Nil
Study population	Inclusion: patients from the Cambridge General Practice Health Study on bone density in the general population (people registered at 12 general practices in Cambridge between 1990 and 1995) who were between 45 and 76 years old and, in 2001, invited to participate (completing a questionnaire and physical assessment including blood samples) Exclusion: patients on a GFD
Control	None
Length of follow-	117 914 patient years (median 16.8)

up

(patients were followed up until the end of 2009)

Details of coeliac testing

IgA EMA (indirect immunofluorescence on commercial monkey oesophagus sections; The Binding Site, Birmingham, UK with 1 in 10 dilution)
Validation with human tTGA was used for all positive samples

Undetected coeliac disease was defined as patients who did not report a diagnosis of coeliac disease and were not on a GFD but had EMA positivity

Results

Of 7550 tested in 2001, 23 were excluded: 3 had probably treated CD (on a GFD and coded as having malabsorption), 1 had probable coeliac disease but untreated (EMA positive, was not on a GFD but was coded as having malabsorption) and 19 with possible coeliac disease (those on a GFD but did not report having a malabsorption and who were EMA negative).

It total, 1.2% (87/7527) of patients were EMA positive

Multivariate logistic regression:

	EMA negative (n=7440)	EMA positive (n=87)	Odds ratio for positive EMA (95% CI)	
			Univariate	Multivariate
Proportion women	59% (4387)	65.5% (57)	1	1
Proportion men	41% (3053)	35.5% (30)	0.76 (0.49-1.18)	0.83 (0.52-1.34)
Age group: < 55 55-64 ≥65	 37.6% (2794) 30.6% (2280) 31.8% (2366)	 42.5% (37) 34.5% (30) 23% (20)	 1 0.99 (0.61-1.61) 0.64 (0.37-1.10)	 1 1.01 (0.62-1.65) 0.67 (0.38-1.16)

Mortality rate:

	Mortality rate per 1000 person years (95% CI)
Women	10.3 (9.6-11.1)
Men	16.2 (15.1-17.4)

Mortality rate by EMA status (using Cox multivariate regression):

	Persons at risk	Deaths	Mortality rate per 1000 person years (95%CI)	Hazard ratio for mortality (95% CI)		
				Unadjusted	Age and gender adjusted	Multivariate adjusted*
EMA negative	7440	1479	12.7 (12.1-13.4)	1	1	1
EMA positive	87	13	9.4 (5.4-16.1)	0.73 (0.42-12.6)	0.91 (0.53-1.58)	0.98 (0.57-1.69)

	* Adjusted for age, gender, socioeconomic group and smoking status Mortality rate attributed to cancer or cardiovascular disease by EMA status (using Cox multivariate regression):

	Mortality rate per 1000 person years (95%CI)		Hazard ratio for mortality (95% CI)					
			Unadjusted		Age and gender adjusted		Multivariate adjusted*	
	EMA negative	EMA positive	EMA negative	EMA positive	EMA negative	EMA positive	EMA negative	EMA positive
Cancer	4.2 (3.8-4.6)	4.3 (1.9-9.6)	1	1.03 (0.46-2.30)	1	1.18 (0.53-2.65)	1	1.27 (0.57-2.85)
Cardiovascular disease	5.1 (4.7-5.5)	5.0 (2.4-10.6)	1	0.99 (0.47-2.08)	1	1.31 (0.62-2.76)	1	1.39 (0.66-2.92)

	* Adjusted for age, gender, socioeconomic group and smoking status
Source of funding	NIHR Clnical Fellowship held by one of the authors and the NIHR Clniical Scientist position held by another author (funding for the original study was from Coeliac UK project grant in 2001)
Conflicts of interest	Study reports no personal interests
Comments	

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

Table 2: Evidence table – Duerksen et al. (2010)

Study type	Non-randomised comparative cross-sectional survey
Country	Canada
Number of patients	N=376 women
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? No - all subjects must have had bone mineral density ANzd coeliac serology - suggests suspicion of CD already apparent in this population 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? No - subjects may have been diagnosed with CD prior to having bone scan - no control for when one had serology and bone scan I.e whether they then became a treated CD patient in GFD at time of bone scan 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? NA

<table>
<tr><td></td><td>
7. What are the results? cD associated with reduced bone mineral density
8. How precise are the results? Precise - low SE but no CI given
9. Do you believe the results? Yes
10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Women with low bone mineral density should be offered testing for CD
</td></tr>
<tr><td>Study population</td><td>
Inclusion: women in the province of Manitoba with CD serology (the Manitoba BMD database was linked to the provincial CD serology database); patients aged 20 years or older at baseline with BMD results preceding serologic testing by 6 months or less

Exclusion: patients with repeat serology (since these individuals often have a diagnosis of CD and serology is monitored to assess the effect of a GFD), patients with repeat BMD after CD serology to minimise any potential confounding effect of a GFD

<table>
<tr><th></th><th>TTG/EMA seronegative cases (n=345)</th><th>TTG/EMA seropositive controls (n=31)</th><th>AGA seronegative cases (n=285)</th><th>AGA seropositive controls (n=371)</th></tr>
<tr><td>Mean age (years)</td><td>62.8±12.4</td><td>55.8±12.1[1]</td><td>62.0±12.8</td><td>62.2±12.4</td></tr>
<tr><td>Weight (kg)</td><td>65.3±15</td><td>65.1±16.3</td><td>65.6±15.4</td><td>65.0±15.0</td></tr>
<tr><td>Height (cm)</td><td>160.0±6.9</td><td>163.1±6.6[1]</td><td>160.1±6.9</td><td>160.8±7.2</td></tr>
<tr><td>BMI (kg/m^2)</td><td>25.5±5.3</td><td>24.5±6.2</td><td>25.6±5.5</td><td>25.1±5.3</td></tr>
</table>
(values are ±SD)
[1] $p < 0.05$, EMA seronegative vs seropositive
</td></tr>
<tr><td>Control</td><td>Individuals with negative serology</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
<tr><td>Details of coeliac testing</td><td>
1996-2007: EMA + AGA
2000-2007: also included TTG
EMA – incubation with human umbilical cord substrate before being used with fluorescein-conjugated guinea pig antihuman immunoglobulin A (positivity if fluorescence is seen at dilutions of 1:5 or greater) (used since 1996 onwards)
AGA – ELISA-based kit (EUROIMMUN, Germany; 20 relative units/mL or greater were considere positive)
From 2000-2003 – guinea pig transglutaminase assay was used but since 2003, TTG were measured using ELISA (EUROIMMUN, Germany; 20 relative units/mL or greater considered positive)
</td></tr>
<tr><td>Results</td><td>
BMD data:
<table>
<tr><th></th><th>TTG/EMA seronegative cases (n=345)</th><th>TTG/EMA seropositive controls (n=31)</th><th>AGA seronegative cases (n=285)</th><th>AGA seropositive controls (n=71)</th></tr>
<tr><td>Mean lumbar spine T score</td><td>–1.98±1.62</td><td>–2.38±1.67</td><td>–1.94±1.70</td><td>–2.24±1.42</td></tr>
</table>
</td></tr>
</table>

	Mean lumbar spine Z score	–0.78±1.55	–1.52±1.64[1]	–0.79±1.61	–1.04±1.45
	Mean total hip T score	–1.35±1.34	–1.79±1.15	–1.29±1.4	–1.69±1.04[1]
	Mean total hip Z score	–0.29±1.27	–1.05±1.13[1]	–0.27±1.32	–0.64±1.06[1]
	Mean femoral neck T score	–1.68±1.07	–1.86±0.82	–1.63±1.12	–1.90±0.83[1]
	Mean femoral neck Z score	–0.26±1.08	–0.74±0.83[1]	–0.24±1.13	–0.49±0.86[1]
	Mean trochanter T score	–1.63±1.31	–2.18±1.21[1]	–1.58±1.35	–2.00±1.08
	Mean trochanter Z score	–50±1.26	–1.32±1.19[1]	–0.47±1.31	–0.90±1.10
	Proportion osteoporotic (ie. minimum T score < –2.5)	44.8% (152)	67.7% (21) [1]	44.8% (125)	52.1% (37)
	Months between BMD testing and serology	3.1±1.8	2.9±1.8	3.1±1.8	3.1±1.9
	(values are ±SD) [1] p < 0.05, EMA seronegative vs seropositive (dual-energy X-ray absorptiometry measurements were performed with pencil-beam instrument before 2000 (Lunar DPX, GE Lunar, Madison, WI) and using a fan-beam instrument after 2000 (Lundar Prodigy, GE Lunar, Madison, WI)				
Source of funding	Not reported				
Conflicts of interest	Not reported				
Comments	Some of the patients included in this study with EMA positivity who were over 40 may be included in Duerksen et al. (2011)				

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

Table 1: Evidence table – Godfrey et al. (2010)

Study type	Non-randomised comparative cross-sectional study
Country	USA
Number of patients	Cross-sectional: N=16 886 patients 50 years or older who were tested for CD Case control: N=127 patients with seropositivity, N=254 matched seronegative controls
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? No - not clearhow comorbidity was defined. 'List of 100' 4. Was the outcome accurately measured to minimise bias? Yes - CD serology 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes - median FU = 10 years

<table>
<tr><td></td><td>7. What are the results? Older adults with CD had limited comorbidity - except fir bone mineral health where people with undiagnosed CD had poorer bone health
8. How precise are the results? Precise - tight CI
9. Do you believe the results? Yes
10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Undiagnosed CD can lead to reduced bone mineral density</td></tr>
<tr><td>Study population</td><td>Patients 50 years and older from Olmsted county who participated in a prior study of monoclonal gammopathy of undetermined significance and with serum samples obtained between the years of 1995 and 2001 and stored.
Exlusion criteria: known CD diagnosis, inconsistent serum volume for testing
(of 24 727 with serum samples saved, consent was gratned by 18 774 individuals but 34 with known CD and those without sufficient serum samples were excluded leaving 16 886 [90.1%] patients who were screened for CD)
<table>
<tr><td></td><td>Serologically negative (n=254)</td><td>Serologically positive (n=127)</td><td>OR (95% CI)[a]</td></tr>
<tr><td>Age at serum draw</td><td>62.9 (51.9, 87.7)</td><td>63.0 (51.7, 87.7)</td><td>1.19 (0.8, 1.78)</td></tr>
<tr><td>Proportion female</td><td>52% (132)</td><td>51.2% (62)</td><td>0.64 (0.13, 3.14)</td></tr>
<tr><td>Weight (kg) [b]</td><td>N=247 78 (38.9, 142)</td><td>N=125 (44, 120.6)</td><td>0.98 (0.97, 1.00)</td></tr>
<tr><td>Height (cm) [b]</td><td>N=242 166.4 (144.3, 189.7)</td><td>N=123 167.6 (124, 203.2)</td><td>1.01 (0.98, 1.04)</td></tr>
<tr><td>BMI</td><td>N=242 27.4 (17.5, 55.5)</td><td>N=123 26.4 (17.2, 42.9)</td><td>0.94 (0.90, 0.99)</td></tr>
</table>
[a] From conditioned logistic regression retaining matching, [b] recorded weight and height closest to date of serum draw</td></tr>
<tr><td>Control</td><td>2 sero-negative controls for every case and matched by age and gender; controls were taken from (appears that controls were selected from databases of patients at one of two major medical care providers in Olmsted county)</td></tr>
<tr><td>Length of follow-up</td><td>Median 10.3 years after serum samples collected</td></tr>
<tr><td>Details of coeliac testing</td><td>tTGA IgA ELISA (ThermoLab DSX ELISA automated system, INOVA Diagnostics, Inc, San Diego, CA; < 2.0 U/ml was considered negative)
Those with positive tests were tested with EMA an immunofluorescence assay (Beckman Coulter, Inc, Brea, CA)
Undiagnosed CD: presence of tTGA test > 2.0 U/ml with positive EMA test (samples were considered negative if tTGA was between 2 and 4 in addition to the EMA test being negative) (tests were considered indeterminate if the tTGA level was > 4.0 U/ml and the EMA was negative)</td></tr>
<tr><td>Results</td><td>Of 16, 886 serologically tested, 1% (163) tested positive for tTGA and 143 had borderline tTGA levels and were tested with EMA.
N=129 were considered serologically positive (0.8%, 95% CI 0.6, 0.9)
2 seropositives and 278 potential controls did not have authorisation for the emdical records so were excluded</td></tr>
</table>

Of those with seropositivity, 20 were subsequently diagnosed clinically with CD after a median of 10.3 (range 0-12.9) years of follow-up but no seronegative controls were diagnosed with CD.

Associated conditions of undiagnosed coeliac disease (defined as serologically positive) compared to serologically negative controls

	Serologically negative (n=254)	Serologically positive (n=127)	OR (95% CI)*
Osteoporosis	Not reported	Not reported	2.59 (1.32, 5.09)
Cancer**	51 (20.1%)	31 (24.4%)	1.29 (0.77, 2.15)
CD-associated cancer	Not reported	Not reported	2.02 (0.29, 14.38)
Visceral cancer	Not reported	Not reported	1.36 (0.67, 2.77)

* conditional logistic regression retaining the matching
** two in each group had CD-associated malignancy (oesophageal cancer in serologically negative and small bowel lymphoma in serologically positive group)

Association between undiagnosed disease (defined as serologically positive) and mortality:

	HR (95% CI)*	p value
All-cause mortality	0.80 (0.45, 1.41)	0.44
Cancer-related mortality	0.63 (0.16, 2.48)	0.51
Visceral cancer-related mortality	0.79 (0.25, 2.50)	0.68
CD-associated cancer mortality	1.01 (0.14, 7.00)	0.99

* Risk in serologically positive cases compared to serologically negative controls (using Cox PH regression stratified on matched set)

Classic ceoalic disease symptoms in serology positive vs negative patients:

	Serologically negative (n=254)	Serologically positive (n=127)	OR (95% CI)**
Diarrhoea	65 (26.2%)	27 (21.4%)	0.77 (0.46, 1.31)
Weight loss	19 (1.8%)	14 (11.2%)	1.67 (0.79, 3.51)
Abdominal pain	92 (37.2%)	46 (36.2%)	0.96 (0.61, 1.51)
Dermatitis herpetiformis	0	5 (4.0%)	-
Irritable bowel syndrome	31 (12.6%)	13 (10.4%)	0.79 (0.40, 1.54)
Deficient haemoglobin	33 (13.1%)	23 (18.4%)	1.63 (0.86, 3.08)

* based on marginal distributions; does not take into account the matching

	**conditional logistic regression which retains the matching Of the 20 seropositive patients subsequently diagnosed clinically with coeliac disease: <table><tr><th></th><th>Serologically positive (n=20)</th></tr><tr><td>Iron deficiency</td><td>9 (45%)</td></tr><tr><td>Dermatitis herpetiformis</td><td>3 (15%)</td></tr><tr><td>Diarrhoea, weight loss</td><td>3 (15%)</td></tr><tr><td>Screened because of family history</td><td>3 (15%)</td></tr><tr><td>Small bowel lymphoma</td><td>1 (5%)</td></tr><tr><td>Nausea</td><td>1 (5%)</td></tr></table>
Source of funding	Research grants from the NIH (National Centre for Research Resources and NIH Roadmap for Medical Research)
Conflicts of interest	Paper states that there are none
Comments	OR for other associated conditions were reported but this was only extracted for those where they were possibley long-term complications of coeliac disease (known mechanisms) since this study did not perform biopsy to confirm coeliac disease (an inclusion characteristic for studies on conditions associated with coeliac disease)

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

Table 4: Evidence table – Hogen Esch et al. (2011)

Study type	Retrospective case series (with historical control)
Country	Netherlands
Number of patients	N=1038 male-female couples (N=2076 individuals)
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Na 7. What are the results? No relationship between CD and subfertility 8. How precise are the results? Imprecise wide CI 9. Do you believe the results? Not clear

<table>
<tr><td></td><td>10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Nil</td></tr>
<tr><td>Study population</td><td>Couples who visited the fertility clinic of the Leiden University Medical Centre bewteen 2003 and 2009; blood samples which were saved for each individual for 10 years were kept for the purposes of checking for sexually transmitted diseases; none had previouslydiagnosed CD

Exclusion: couples in which there was no serum available to test (Of 1180 couples available, 142 did not have serum to test so 1038 couples were included [88%]).

Patient characteristics (n=1038)
<table>
<tr><td></td><td>Females</td><td>Males</td></tr>
<tr><td>Medan age (range)</td><td>32.3 (20-45)</td><td>35.4 (20-64)</td></tr>
<tr><td>Median BMI in kg/m^2 (range)[a]</td><td>N=798 23.3 (16-49)</td><td>N=590 25.4 (18-48)</td></tr>
</table>
[a] BMI not measured in all

Prevalence by causes of subfertility:
(69% of those included were examined for primary subfertility and 31% for secondary subfertility)
<table>
<tr><td></td><td colspan="2">Study group (n=2076)</td><td colspan="2">Unrecognised CD (seropositive) (n=10)</td></tr>
<tr><td></td><td>Females (n=1038)</td><td>Males (n=1038)</td><td>Females (n=6)</td><td>Males (n=4)</td></tr>
<tr><td>Ovulation disorder</td><td>20% (203)</td><td>n/a</td><td>1.48% (3)</td><td>n/a</td></tr>
<tr><td>Tubal factor</td><td>10% (100)</td><td>n/a</td><td>0</td><td>n/a</td></tr>
<tr><td>Male factor</td><td>n/a</td><td>45% (464)</td><td>n/a</td><td>0.22% (1)</td></tr>
<tr><td>Partners of subject with particular subfertility diagnosis</td><td>37% (384)</td><td>22% (223)</td><td>0.26% (1)</td><td>0.45% (1)</td></tr>
<tr><td>Unexplained</td><td>34% (351)</td><td>34% (351)</td><td>0.57% (2)</td><td>0.57% (2)</td></tr>
</table></td></tr>
<tr><td>Control</td><td>Rate of unrecognised CD was compared in the study participants to those in the general population (from a published screening study from the same authors)</td></tr>
<tr><td>Length of follow-up</td><td>n/a</td></tr>
</table>

Details of coeliac testing

IgA anti-tTG type 2 (ELIA™ Celikey® assay at the Immunocap® 250 system using human recombinnant tissues transglutaminase as an antigen, Phadia GmbH, Freiburg, Germany; >10 U/mL is positive and 7-10 U/mL is equivocal area)
IgA EMA using monkey's oesophagus as substrate (dilution1:10) according to manufacturer (Scimedx)

Unrecognised CD was defined if tests results for both were positive in one subject. (authors stated that this accurately predicts the presence of subtotal villous atrophy) (small bowel biopsies were not offered to the subjects)

(control subjects were tested similarly but for IgA anti-TG2 using a guinea pig substrated from in house developed ELISA)

Results

12 samples had positive IgA anti-TG2 levels considered positive for CD (0.6%; median 60 U/ml, range 13-137)
IgA-EMA was positive in 10/12 of those positive for IgA anti-TG2 (83%)

Prevalence of unrecognised CD (defined as seropositivity)	Study group of subfertile couples	Control group [a]	OR (95% CI) [b]
Overall	**0.48% (10/2076) of individuals [c]**	**0.35% (5/1432)**	**1.38 (0.471, 4.05)**
In females	0.58% (6/1038)	0.28% (2/716)	2.08 (0.42, 10.31)
In males	0.39% (4/1038)	0.42% (3/716)	0.92 (0.21, 4.12)
Females with unexplained subfertility in females	0.57% (2/351)	0.28% (2/716)	2.05 (0.29, 14.58)
Males with unexplained subfertility	0.57% (2/351)	0.42% (3/716)	1.35 (0.23, 8.19)
Females with an ovulation disorder	1.48% (3/203)	0.28% (2/716)	5.36 (0.89, 32.27)
Subfertility due to male factor	0.22% (1/464)	0.42% (3/716)	0.51 (0.05, 4.95)

[a] from previous study described above under 'control', [b] Fisher's exact test, [c] in no couples did both partners have unrecognised CD

Of the 10 subjects in the study group with unrecognised CD:

	Females (n=6)	Males (n=4)	Significance
Mean age (SD)	29 (±5.3)	36 (±3.1)	NS
Mean BMI in kg/m^2 (range)[a]	N=4 25.4 (±2.9)	N=2 24.5 (±0)	NS

[a] BMI not measured in all

Source of funding

Dutch Celiac Disease Consortium and the Gratama-LUF research foundation. ELIA™ Celikey® assays were supported partly from the manufacturer.

Conflicts of interest

Not reported

Comments

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

Table 5: Evidence table – Jafri et al. (2008)

Study type	Case control
Country	USA
Number of patients	N=83 with CD N=166 matched controls without CD
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? No - not clear if age accounted for and the taking of calcium supplements 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes 7. What are the results? May be increased Fracture risk in those with undiagnosed CD 8. How precise are the results? Imprecise wide CI 9. Do you believe the results? No, results lie on line of no effect 10. Can the results be applied to the local population? Not clear 11. Do the results fit with other available evidence? Yes, moderately 12. What are the implications of this study for practice? Not clear
Study population	Olmsted County (Minnesota) residents with coeliac disease (confirmed by standard clinical and histologic criteria) Median age: 46 years (range 1 to 84) 70% female (58) Mean period of observation between date of the first registration and the diagnosis date (or date of closest clinical visit for controls) was 9.7 years in both groups with 5.1 year median follow-up for cases and 4.5 years for controls.
Control	2 per patient taken from among Olmsted County (Minnesota) residents and matched by age (+/- 2 years), sex, and closest clinical number
Length of follow-up	Length of time which participants' histories were tracked was not reported. However, complete inpatient and outpatient records at each local provider were checked for occurrence of fracture (author states that medical records for those in Olmsted County are held in central database)

<table>
<tr><td>Details of coeliac testing</td><td>Authors state that coeliac disease was confirmed by standard clinical and histologic criteria (no other details provided)</td></tr>
<tr><td>Results</td><td>Fracture risk before diagnosis:
<table>
<tr><th>Fracture type</th><th>Unadjusted HR (95% CI)</th><th>p value</th><th>Adjusted HR (95% CI) [a]</th><th>p value</th></tr>
<tr><td>Any</td><td>2.0 (1.0, 3.9)</td><td>0.045</td><td>2.0 (1.0, 3.9)</td><td>0.044</td></tr>
<tr><td>Peripheral</td><td>2.0 (1.0, 3.8)</td><td>0.052</td><td>2.0 (1.0, 3.9)</td><td>0.054</td></tr>
<tr><td>Axial</td><td>1.7 (0.7, 4.1)</td><td>0.273</td><td>1.7 (0.7, 4.2)</td><td>0.258</td></tr>
<tr><td>Osteoporotic</td><td>8.0 (0.9, 72)</td><td>0.063</td><td>6.9 (0.7, 65)</td><td>0.093</td></tr>
</table>
(all odds ratios are patients with coeliac vs controls) (unclear if authors have used correct calculation of OR for matched study designs)
[a] adjusted for Charlson comorbidity index (a weight index which takes into account the number and seriousness of 17 chronic comorbid diseases)</td></tr>
<tr><td>Source of funding</td><td>Research grants from the University of Rochester General Clinical Research Centre from the National Institutes of Health, US Public Health Service</td></tr>
<tr><td>Conflicts of interest</td><td>Not reported (however, the authors state the funding source had no role in the design or executive of the study)</td></tr>
<tr><td>Comments</td><td>Diagnosis of ostopenia or osteoporosis was significantly more prevalent in cases than controls (17% vs 7%, p=0.016) but rates of thyroid disease were not significantly different; .</td></tr>
</table>

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

Table 6: Evidence table – Kumar et al. (2011)

Study type	Case-control
Country	India
Number of patients	N=588 women - 104 with idiopathic recurrent abortion - 104 with unexplained still birth - 230 with infertility - 150 pregnant women with idiopathic intrauterine growth restriction (IUGR) N=305 control
Quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes

	6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes 7. What are the results? CD is associated with high rates of unexplained fertility 8. How precise are the results? Imprecisev- wide CI 9. Do you believe the results? Yes, however the estimation of prevalence if CD in this population is much higher than expected 10. Can the results be applied to the local population? Yes 11. Do the results fit with other available evidence? Yes, however see 9 12. What are the implications of this study for practice? Women with unexplained poor pregnancy outcomes should be considered for testing for CD
Study population	Inclusion (for all): Consecutive women with a history of idiopathic recurrent spontaneous abortion, history of unexplained still birth, unexplained infertility and idiopathic intrauterine growth restriction attending a tertiary teaching hospital in New Delhi between August 2006 and July 2009 *Inclusion for infertility*: normal semen analysis from the husband, normal ovulation assessed by premenstrual endometrial biopsy, normal postcoital test result (for cervical factor of infertility), normal serum LH, FSH, and PRL, normal tubal patency, normal diagnostic laparoscopy *Inclusion for IUGR:* discrepancy of > 4 weeks between fundal height of uterus and period of gestation in weeks in the 3rd trimester and observed on 2 successive antenatal visits; subsequently, if measured was < 4 cm from expected height of the uterus, inappropriate fetal growth was suspected (exclusion: hypertension in pregnancy, congenital malformation in the fetus, heart disease, renal disease, smoking, known metabolic disorder) *Inclusion for recurrent spontaneous abortion:* 2 or more clinically recognised pregnancy losses before 20 weeks from the last menstrual period (exclusion: single spontaneous abortion (anatomic, hormonal, chromosomal, autoimmune, or infection) *Inclusion for stillbirth:* birth of the newborn after 28 completed weeks of gestation with no signs of life after delivery (exclusion: identifiable causes of stillbirth like preeclapsia, hypertension, diabetes mellitus, uteroplacental insufficiency Of 125 women with recurrent spontaneous abortion, 118 with stillbirth, 170 with IUGR, and 250 with infertility: - 15 refused consent (7 with spontaneous abortion, 5 with stillbirth, 3 with unexplained infertility) - 14 more with spontaneous abortion were excluded because they had other conditions (6 with hypothyroidism, 7 with diabetes, 1 with antiphospholipid antibody syndrome) - 9 more with stillbirth were excluded because they had diabetes, - 20 more with IUGR were excluded because they had other conditions (10 with preeclampsia, 6 with heart disease, 4 with chronic renal disease) - 17 more with infertility (4 with male factor infertility, 6 with polycystic ovary disease, 6 with bilateral tubal block and 1 with hypothyroidism)

	Recurrent abortion (n=104)	Stillbirth (n=104)	Infertility (n=230)	IGUR (n=150)	Control (n=305)
Mean age in	26.47±3.80	26.87 ± 3.54	29.71 ± 4.64	28.31 ± 4.00	27.75 ± 4.48

	years (± SD)					
	Mean BMI (kg/m^2) (± SD)	22.36 ± 3.24	23.86 ± 3.55	23.44 ± 4.00	22.68 ± 4.03	21.08 ± 3.54
Control	Women with normal obstetric history who attended the family planning clinic of the hospital					
Length of follow-up	n/a (until delivery for those with IGUR)					
Details of coeliac testing	Of serum taken at the time of recruitment and stored at –20°C, all samples were analysed for IgA anti-tTG (≥ 5 U/mL was positive), IgA AGA (≥ 20 RU/mL was positive), and IgG AGA (≥ 30 RU/mL was positive) (ELISA, Radim SpA, Pomezia, Italy) and IgA EMA by indirect immunofluorescent microscopy with use of fixed cryostat sections of monkey oesoagphus (The Binding Site, Birmingham, UK)					

Results

	Recurrent abortion (n=104)		Stillbirth (n=104)		Infertility (n=230)		IGUR (n=150)		Control (n=305)
	% seropositive (n)	p value (vs control)	% seropositive (n)	p value (vs control)	% seropositive (n)	p value (vs control)	% seropositive (n)	p value (vs control)	% seropositive
IgA tTG	6.7 (7)	0.007	5.7 (6)	0.02	5.65 (13)	0.004	9.33 (14)	0.0001	1.31 (4)
IgA AGA	5.7 (6)	0.02	13.4 (14)	0.0002	13.04 (30)	0.0001	30.7 (46)	0.0001	1.31 (4)
IgG AGA	20.19 (21)	0.0001	9.6 (10)	0.24	12.6 (29)	0.01	16 (24)	0.0008	6.23 (19)
IgA EMA	4.81 (5)	0.03	4.81 (5)	0.03	4.78 (11)	0.006	6.67 (10)	0.001	0.98 (3)

On the basis of tTG:

	Recurrent abortion (n=104)	Stillbirth (n=104)	Infertility (n=230)	IGUR (n=150)
OR vs control group (95% CI)	5.43 (1.34, 25.72)	4.61 (1.06, 22.56)	4.51 (1.36, 19.19)	7.75 (2.36, 32.76)

(the seroprevalence of the IgA tTG and IgA EMA was similar between all the groups, p > 0.05)

Pregnancy and labour complications:

	Recurrent abortion (n=104)			Stillbirth (n=104)			IGUR (n=150)		
	% seropositive (n)	% seronegative (n)	p value	% seropositive (n)	% seronegative (n)	p value	% seropositive (n)	% seronegative (n)	p value
History of pre-term delivery*	42.9 (3)	10.3 (10)	0.04	33.3 (2)	14.3 (14)	0.23	42.8 (6)	6.6 (9)	< 0.0001

	History of low birth weight infants	85.7 (6)	5.2 (5)	< 0.0001	83.3 (5)	19.4 (19)	0.002	35.7 (5)	14.7 (20)	0.06
	History of caesarean section**	85.7 (6)	13.4 (13)	< 0.0001	100 (6)	10.2 (10)	< 0.0001	57.1 (8)	9.6 (13)	< 0.001
	* < 37 weeks ** all caesarean sections were performed for obstetric indications									
Source of funding	Indian Council of Medical Research, New Delhi									
Conflicts of interest	Paper reports that all the author have nothing to disclose									
Comments	Authors also compared the prevalence in anaemia in women in these groups but this has not been reported here									

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

Table 2: Evidence table –Leboff al. (2011)

Study type	Case control
Country	USA
Number of patients	N=208 (81 from Boston, 127 from Baltimore) N=51
	Leboff 2013 - **poor : no to both screening questions** 1. Did the study have a clearly focused aim? No - many different sub questions. 2. Was the cohort recruited in an acceptable way? No - no consecutive recruitment 3. Was the exposure accurately measured to minimise bias? 4. Was the outcome accurately measured to minimise bias? 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? 7. What are the results? 8. How precise are the results? 9. Do you believe the results? 10. Can the results be applied to the local population? 11. Do the results fit with other available evidence?

	12. What are the implications of this study for practice?
Study population	Inclusion: Community dwelling women with hip fracture recruited between 1995 and 1998 (Boston) or between 1992 and 1995 (Baltimore) Exclusion: other medications or any disorders or abnormal admission test results that might affect bone, or had any underlying hip disease other than osteoarthritis; women with high-energy, pathological fractures or not community-dwelling at the time of fracture

	Hip fracture			Control*	p value of total hip fracture vs control
	Boston (N=30)*	Baltimore (n=127)**	Total (n=157)		
Mean age (± SD)	77.9 ± 9.2	80.8 ± 7.9	80.3 ±8.1	64.4 ± 8.1	< 0.0001
Race (% Caucasian)	91%	96%	95%	97%	NS

*these women were part of a larger study of 98 women with no other secondary cause for osteoporosis aside from possible vitamin D deficiency
**these women were part of a larger study of 205 women with acute hip fractures

Control	Women with elective hip replacement without osteoporosis (selected from a larger study in Boston)
Length of follow-up	n/a
Details of coeliac testing	The following was tested in serum which was taken and stored at –6°C: tTG-IgA (ELISA where normal < 1 U) If tTG-IgA normal, serum total IgA was measured (ELISA; normal70-400 mg/dl) If Iga was low, tTG-IgG (where normal ≥ 26 U) was measured
Results	Proportion with seropositivity for coeliac disease:

	Hip fracture			Control	p value of total hip fracture vs control
	Boston (N=30)	Baltimore (n=127)	Total (n=157)		
Seropositivity	3.33% (1)	1.57% (2)	1.91% (3)	1.96% (1)	NS

(patients with hip fractures had significantly lower vitamin D levels than the control group: median 14 ng/ml 25-hydroxyvitamin D compared with median 21.3 ng/ml in the control group, p < 0.0001)

Source of funding	Various National Institutes of Health grants, the National Center for Research Resources, General Clinical Research Centre (Brigham and Women's Hospital), Connors Award at Brigham and Women's Hospital, Claude D. Pepper Older Americans Independence Centre
Conflicts of interest	Authors reported no competing interests

Comments	

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

Table 3: Evidence table – Lohi et al. (2009b)

Study type	Non-randomised comparative cross sectional survey
Country	Finland
Number of patients	N=6849 Finnish adults
quality	1. Did the study have a clearly focused aim? Yes 2. Was the cohort recruited in an acceptable way? Yes 3. Was the exposure accurately measured to minimise bias? Yes 4. Was the outcome accurately measured to minimise bias? Yes 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes - up to 20 years 7. What are the results? No increased malignany in those with undiagnosed CD 8. How precise are the results? Precise tight CI 9. Do you believe the results? Yes 10. Can the results be applied to the local population? Yes 11. Do the results fit with other available evidence? Yes 12. What are the implications of this study for practice? Nil
Study population	The Mini-Finland Health Survey in 1978-80, a nationally representative sample of 8000 persons from the population between 30 and 99 years old adults; participation rate was 90% (7217) and sera from 6990 individuals were available for this study Exclusion: previous diagnosis of coeliac disease or dermatitis herpetiformis (3 excluded for this reason) mean 51 years (range 30-95) 3680 females
Control	Patients from the sample with negative serology
Length of follow-up	n/a
Details of coeliac testing	Sera were stored at –20 °C and analysed for immunoglobulin A (IgA)-class tTG (Eu-t TG® umana IgA, Eurospital, Trieste, Italy); if positive, sera were analysed for both IgA EMA (a characteristic staining pattern at serum dilution 1:≥5 was considered positive) and another IgA tTG (Celikey®, Phadia, Freiburg, Germany) (for Eu-tTG, 7.0 AU/mL was the cut-off and for Celikey tTG, 5.0 AU/mL was the

	cut-off) (Celikey tTG and EMA was used in 128 randomly selected Eu-tTG-negative patients as there was an unexpectedly high Eu-tTG positivity in the sera for the Mini-Finland survey collected 22 years earlier)
Results	Results from serological testing: Eu-tTG-positives: 82% (565/6849) EMA positive: 12.9% (73/565) of Eu-tTG positives (52 females, mean age 50 years) or 10.6% (73/6849) of all patients Celikey tTG positive: 35.8% (202/565) (129 females, mean 59 years) of Eu-tTG positives or 29.5% (202/6849) of all patients

	Relative risk [a]					
	Celikey tTG negativity (95% CI) N=6647	Celikey tTG positivity (95% CI) N=202	p value	EMA negativity (95% CI) N=6776	EMA positivity (95% CI) N=73	p value
All cancer	1.00 (n=671)	0.91 (0.60, 1.37) (n=23)	0.64	1.00 (n=689)	0.67 (0.28,1.61) (n=5)	0.33
Lymphoproliferative diseases	1.00 (n=28)	2.76 (0.83, 9.16) (n=3)	0.15	1.00 (n=29)	**5.94 (1.41, 25.04) (n=2)**	**0.05**
Gastrointestinal cancer	1.00 (n=115)	1.38 (0.60, 3.14) (n=6)	0.47	1.00 (n=121)	0 (n=0)	0.12
Lung cancer	1.00 (n=83)	0.73 (0.18, 2.97) (n=2)	0.64	1.00 (n=85)	0 (n=0)	0.26
Breast cancer	1.00 (n=89)	0.64 (0.16, 2.59) (n=2)	0.49	1.00 (n=90)	0.71 (0.10, 5.07) (n=1)	0.71
Prostate cancer	1.00 (n=56)	0.54 (0.07, 3.90) (n=1)	0.50	1.00 (n=57)	0 (n=0)	0.41

[a] adjusted for sex and age

Source of funding	The Coeliac Disease Study Group is funded by grants from the Competitive Research Funding of the Pirkanmaa Hospital District, the Emil Aaltonen Foundation, the Foundation for Paediatric Research, the Yrjö Jahnsson Foundation, the Finnish Coeliac Society, and the Academy of Finland, Research Council for Health; this study was also funded by the Commission of the European Communities (with a Research and Technology Development programme 'Quality of Life and Management of Living Resources', 'Evaluation of the Prevalence of Coeliac Disease and its Genetic Components in the European Population')
Conflicts of interest	The authors report no conflicts of interest
Comments	

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

Table 4: Evidence table –Sánchez et al. (2011)

<table>
<tr><td>Study type</td><td>Cross-sectional data from cohort study</td></tr>
<tr><td>Country</td><td>Argentina</td></tr>
<tr><td>Number of patients</td><td>N=265 adults (223 female and 42 male) with a diagnosis of coeliac disease
N=530 controls</td></tr>
<tr><td>Quality</td><td>1. Did the study have a clearly focused aim? Yes - 2 clear aims
2. Was the cohort recruited in an acceptable way? No - not clear recruitment strategy
3. Was the exposure accurately measured to minimise bias? No - questionnaire data highly biased
4. Was the outcome accurately measured to minimise bias? Yes CD clearly defined
5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? No - many important confounding factors, namely memory bias and personal recollection bias, no supporting info source
6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Na
7. What are the results? CD group showed higher incidence rate of fracture
8. How precise are the results? Precise - tight CI
9. Do you believe the results? No - questionnaire data nit appropriate way of addressing research aim
10. Can the results be applied to the local population? Not clear
11. Do the results fit with other available evidence? Yes
12. What are the implications of this study for practice? Not clear</td></tr>
<tr><td>Study population</td><td>Patients who attended gastroenterology units in four medical centres from March 2007 to November 2009

Inclusion: diagnosis confirmed at least 5 years prior to entry into the study

Exclusion: patients diagnosed with other disorders that could independently reduce bone health (ie. uncontrolled thyroid dysfunction, rheumatoid arthritis, inflammatory bowel disease, diabetes), who took medications that could affect bone metabolism (ie. steroids, calcium, vitamin D, alendronate, anticonvulsants, thyroid hormones, estrogen or androgen replacement) and who had complicated CD.

<table>
<tr><td></td><td>Coeliac disease
(N=265)</td><td>Control
(N=530)</td><td>p value</td></tr>
<tr><td>Proportion female</td><td>84% (223)</td><td>84% (530)</td><td rowspan="3">Not reported</td></tr>
<tr><td>Median age (range)</td><td>42 (18-85)</td><td>43 (16-87)</td></tr>
<tr><td>Median age at diagnosis (range)</td><td>30 (1-80)</td><td>-</td></tr>
</table>
</td></tr>
</table>

	Mean BMI (kg/m^2) ±SE	22.5 ± 0.2	24.3 ±0.2	0.001
	Median age at menarche (range)	13 (9-17)	12 (9-20)	Not reported
	Median age at menopause (range)	48 (30-54)	49 (36-59)	
Control	2 age and sex matched controls (for each patient with CD) with functional gastrointestinal disorders (based on Rome III criteria)			
Length of follow-up	Person-years before diagnosis: 7028 (cases) vs 14532 (controls (of cases 6480 were attributed to females and 647 males)			
Details of coeliac testing	Based on combination of positive clinical findings (symptoms or risk factors such as family history), characteristic enteropathy at the time of diagnosis, positive CD0speicifc serology and positive clinical and/or histological response to GFD; positive serological tests (antigliadin antibodies, anti-tissue transglutaminase antibodies and/or antimysium antibodies) were considered sufficient for a diagnosis of CD			
Results	Fracture rate before diagnosis:			

	Coeliac disease (N=265)	Control (N=530)
Proportion of patients with at least one fracture	15.1% (40)	8.5% (45)
Median age at first fracture (range)	10 (2-61)	15 (1-74)

(Asked by questionnaire of patients and confirmed in patient records)

Characteristics of patients with coeliac disease:

	Female (N=223)	Male (N=42)	p value
Median age (range)	42 (18-62)	35 (18-66)	0.04
Median age at diagnosis (range)	31 (1-80)	19 (1-52)	0.003
Mean BMI (kg/m^2) ±SE	22.5 ± 0.5	23.7 ±0.6	0.01
Proportion with at least one fracture before diagnosis	13% (29)	26% (11)	0.05
Median age at first fracture before diagnosis (range)	14 (2-61)	10 (6-32)	0.04

Risk of fracture

	Coeliac disease (N=265)	Control (N=530)	HR (95% CI) p value	Adjusted HR (95% CI)
All - incidence ratio	8.67	5.64	1.53 (1.05-2.14), p=0.01	1.78 (1.23-2.56)*, p=0.02
Females – incidence ratio	6.58	5.09	1.28 (0.87-1.88), p=NS	1.52 (0.99-2.32)*, p=0.052

	Males – incidence ratio	29.35	10.20	2.67 (1.37 -5.22), p=0.004	2.63 (1.24-5.59)*, p=0.01
	* adjusted by age at enrolment, age at diagnosis, BMI, smoking habits and menopause				
Source of funding	Partially from Asociacion para el estudio de las Enfermedades del Intestino				
Conflicts of interest	Not reported				
Comments	Authors included any events occuring during the first year after diagnosis of coeliac disease in the 'before diagnosis' category because coeliac disease is a long-term disease and GFD may only provide a slow recovery				

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

Table 5: Evidence table – Silano et al. (2007)

Study type	Retrospective case series
Country	Italy
Number of patients	N=1968
Study population	Patients diagnosed with CD (with NIH criteria including histological evidence of atrophy of small bowel mucosa and serological positivity for EMA and/or anti-tTG Ab) at 20 Italian gastroenterology referral Centres beween 1st January 1982 and 31st March 2005. 1485 female (female/male ratio: 2.6) Mean age at diagnosis of CD: 36.2 ± 13.8 years
Quality	Silano 2007 in **prev guideline: check QA** 1. Did the study have a clearly focused aim? 2. Was the cohort recruited in an acceptable way? 3. Was the exposure accurately measured to minimise bias? 4. Was the outcome accurately measured to minimise bias? 5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? 6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? 7. What are the results? 8. How precise are the results? 9. Do you believe the results? 10. Can the results be applied to the local population? 11. Do the results fit with other available evidence?

	12. What are the implications of this study for practice?
Control	none
Length of follow-up	Mean duration of symptoms before diagnosis 6 ± 2 years
Details of coeliac testing	No details provided (apart from that histological evidence of atrophy in the small bowel mucosa and serological postiivitiy for EMA and/or anti-tTG Ab were required for a diagnosis of CD)
Results	**55 (2.09%) were diagnosed with cancer before or simultaneously at the diagnosis of CD**

Malignancies observed	Number of malignancies observed	Number of malignancies expected [a]	SIR (95% CI)	p value
Higher risk in CD patients				
Non-Hodgkin's lymphoma	20	4.2	4.7 (2.9-73)	<0.001
Colon	7	6.2	1.1 (0.68-1.56)	<0.001
Small bowel	5	0.19	25 (8.5-51.4)	<0.001
Hodgkin's lymphoma	4	0.4	10 (2.7-25)	0.01
Stomach	3	1	3 (1.3-4.9)	0.08
Lower risk in CD patients				
Breast	3	14	0.2 (0.04-0.62)	<0.001
Other	13	12	1 (0.9-8.5)	0.06
Total	55	42.1	1.3 (1.0-1.7)	0.001

[a] based on specific incidence rate from WHO Globescan 2002 adjusted for the sex and age of the population

The mean age at diagnosis of coeliac disease for those diagnosed with cancer before or simultaneously 47.6±10.2yrs which was significantly higher than the age at diagnosis of those who did not develop a malignancy 28.6±18.2yrs

Source of funding	Not reported
Conflicts of interest	Study reports that there are none
Comments	Authors conclucded that coeliac patients have an increased risk of developing cancer in relation to the age of diagnosis of CD and this result it higher for malignancies of gastro-intestinal sites

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

Table 6: Evidence table – Zugna et al. (2013)

<table>
<tr><td>Study type</td><td>Case control</td></tr>
<tr><td>Country</td><td>Sweden</td></tr>
<tr><td>Number of patients</td><td>N=12,919 children born to mothers with undiagnosed CD
N=53,186 children used as controls
N=3202 children born to mothers with diagnosed CD</td></tr>
<tr><td>Quality</td><td>1. Did the study have a clearly focused aim? No - many different sub questions and populations embedded in study
2. Was the cohort recruited in an acceptable way? Yes
3. Was the exposure accurately measured to minimise bias? Difficult to determine how mortality was defined - mortality at birth? Or throughout childhood? Or both?
4. Was the outcome accurately measured to minimise bias? Yes
5. Have the authors identified all important confounding factors? Have they taken account of confounding factors in the design/analysis? Yes
6. Was the follow-up of subjects complete enough? Was the follow-up of subjects long enough? Yes
7. What are the results? No increased mortality in children born to mothers with undiagnosed CD
8. How precise are the results? Imprecise
9. Do you believe the results? Yes
10. Can the results be applied to the local population? Yes
11. Do the results fit with other available evidence? Not clear
12. What are the implications of this study for practice? Not clear</td></tr>
<tr><td>Study population</td><td>Children born to women with undiagnosed CD who gave birth to a live singleton infant between 1961 and 2009 taken from computerised biopsy report data from all Swedish pathology departments

Of all mothers with CD (diagnosed or undiagnosed):
<table>
<tr><th></th><th>With CD
(16, 121 births)</th><th>Without CD
(61, 782 births)</th></tr>
<tr><td>Sex of child</td><td>50.7% (8179) male</td><td>51.3% (31, 712) male</td></tr>
<tr><td>Mothers with type I diabetes</td><td>1.4% (227)</td><td>0.3% (175)</td></tr>
<tr><td>Mothers with thyroid disease</td><td>7.7% (1239)</td><td>2.9% (1807)</td></tr>
<tr><td>Mothers with rheumatoid arthritis</td><td>1.3% (206)</td><td>0.8% (466)</td></tr>
<tr><td>Non-smoking mothers</td><td>39.6% (6378)</td><td>37.4% (23, 085)</td></tr>
</table>
</td></tr>
</table>

Control

5 per patient matched for age, sex, calendar year of birth and county of residence taken asa sample of all Swedish residents (data from Statistics Sweden) with no prior duodenal or jejunal biopsy (exclusion: those with a duodenal or jejunal biopsy during following, those who died before the hypothetical biopsy date [based on those of the matched index], and those whose matched index case with CD was excluded)

Length of follow-up

n/a

Details of coeliac testing

Not described

Results

Risk of death in children born to mothers with undiagnosed CD or no CD:

	Crude HR (95% CI)	Adjusted HR (95% CI) [a]
No CD	1.0	1.0
Undiagnosed CD	1.10 (0.95, 1.26) [b]	1.08 (0.94, 1.25) [b]

(unclear if authors have used correct calculation of OR for matched study designs)

[a] adjusted for maternal age, maternal country of birth, maternal educational level, maternal total number of children, infant's year of birth (calendar year of birth, appearance of maternal diabetes, thyroid disease and rheumatoid arthritis were all considered as time-dependent variables in the models)

[b] no difference between male and female children

Risk of nonaccidental death in children:

	HR (95% CI)*
Undiagnosed CD	1.07 (0.92, 1.26)
Diagnosed CD	1.30 (0.65, 2.58)

* unclear if this HR is adjusted

Risk of death in children (5 year follow-up only):

	HR (95% CI)*
Undiagnosed CD	1.23 (0.99, 1.54)
Diagnosed CD	1.22 (0.60, 2.48)

* unclear if this HR is adjusted

Risk of death in children (children born from 1982 onwards):

	Adjusted HR (95% CI)*
Undiagnosed CD	1.27 (0.80, 2.00)

	<table><tr><td>Diagnosed CD</td><td>1.12 (0.54, 2.32)</td></tr></table> * adjusted for prenatal smoking exposure and civil status Post hoc analysis of risk of death in children (restricted to the first year of follow-up only): <table><tr><td></td><td>HR (95% CI)*</td></tr><tr><td>Undiagnosed CD</td><td>0.74 (0.30, 1.85)</td></tr><tr><td>Diagnosed CD</td><td>1.32 (1.03, 1.67)</td></tr></table> * unclear if this HR is adjusted
Source of funding	One author was partially supported by grants from The Campagnia san Paolo/Firms and the Italian Association for Cancer Research, 2 authors were supported by the Swedesh Society of Medicine, and one was supoorted by the Swedish Society of Medicine, the Swedish Research Council-Medicine, the Swedish Celiac Society,and the Fulbright Commission (authors state that none of the funders had any role in the design or conduct of the study, in the collection, management, analysis and interpretation of data, or in the preparation, review or approval of the manuscript)
Conflicts of interest	None declared
Comments	

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

Abbreviations

BMD – bone mineral density

CD – coeliac disease

CI – confidence interval

EATL – enteropathy-associated T-cell lymphoma

EMA – anti-endomysial antibodies

FSH – follicle-stimulating hormone

GFD – gluten-free diet

HR – hazard ratio

IQR – intraquartile range

IRR – incidence rate ratio

LH - luteinizing hormone

NIH – National Institute of Health (USA)

PCR – polymerase chain reaction

SD – standard deviation

SIR – standardised incidence ratio (ratio of the observed to the expected cases)

SMR – standardised mortality rate

TCR – T-cell receptor

anti-tTG – anti-transglutaminase antibodies

UJ – ulcerative jejunitis

D.4 Review question 4.4

Bibliographic reference	No studies were identified for this question
Study type	
Study quality	
Number of patients	
Patient characteristics	
Intervention	
Comparison	
Length of follow up	
Location	
Outcomes measures and effect size	
Source of funding	
Comments	*No studies were identified for this question*

(a) No studies identified

D.5 Review questions 5.1 & 5.2

Bibliographic reference	Burgin-Wolff (2013): Intestinal biopsy is not always required to diagnose coeliac disease: a retrospective analysis of combined antibody tests
Study type	Cohort (retrospective)
Study quality	1. Could the selection of patients have introduced bias? NO – consecutive patients recruited 2. Is there concern that the included patients do not match the review question? NO – all patients suspected of CD 3. Could the conduct or interpretation of the index test have introduced bias? NO – N/A 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO – index test as specified in protocol 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – target condition matches review question 7. Could the patient flow have introduced bias? YES – 'For an undefined period of time patients were sometimes selected for biopsy when IgA tTG or EMA were positive' **Overall risk of bias**
Number of patients	Total N=268 adults and children
Patient characteristics	Inclusion: adults and children with symptoms suggestive of CD on a gluten containing diet. All patients who received a jejunal biopsy and serology testing were included Exclusion: participants who were IgA deficient
Intervention	All samples analysed by fully automated fluoroenzyme immunoassay tests (Elia Celikey IgA, Elia Gliadin IgA, Elia Gliadin IgG, Elia Gliadin DGP IgA, Elia Gliadin DGP IgG) EMA was analysed by indirect immunofluorescence on monkey oesophagus sections Optimal cut-off values calculated using ROC curves. For all samples, except IgA DGP, best sensitivity and specificity were found to be consisted with manufacturer's recommendations.

Bibliographic reference	Burgin-Wolff (2013): Intestinal biopsy is not always required to diagnose coeliac disease: a retrospective analysis of combined antibody tests
	I. IgA tTG – cut off =7 II. IgA AGA – cut off = 7 III. IgG AGA – cut off = 7 IV. IgA DGP – cut off =7 [a] V. IgG DGP – cut off = 10 VI. IgA EMA – cut off = serum dilution 1:5
Comparison	Jejunal biopsy – no other information. [b]
Length of follow up	
Location	Switzerland
Outcomes measures and effect size	Diagnostic accuracy of serological tests CI: 95%
Source of funding	
Comments	

[a] Authors found a cut off value of 7 instead of 10 increased sensitivity from 71% to 78%, while maintaining specificity
[b] For an undefined period, patients were sometimes selected for biopsy when IgA tTG or EMA were positive

Total N= 149/268 (56%) diagnosed with CD according to Marsh Classification (Marsh 3a, b, or c lesions accepted).

Sensitivity, specificity, PPV, NPV, and efficiency, and positive and negative likelihood ratio data were provided in the paper.

IgA DGP in children and adults
Sensitivity 78% (71 – 85), specificity 97 % (93 – 99), PPV 97% (93 – 99), NPV 78% (71 – 84), efficiency 86%, + LHR = 23. – LHR = 0.23

(a)TP 116	(b)FP 4
(d)FN 33	(c)TN 115

IgG DGP in children and adults
Sensitivity 85% (80 – 90) specificity 92% (86 – 97), PPV 93% (88 – 97), NPV 83% (77 – 90), efficiency 88%, +LHR = 10, -LHR = 0.16

(a)TP 127	(b)FP 10

(d)FN 22	(c)TN 109

IgA tTG in children and adults
Sensitivity 97% (94 – 99) specificity 87% (80 – 92), PPV 90% (85 – 95), NPV 95% (91 – 99), efficiency 92%, +LHR = 7, -LHR = 0.04

(a)TP 144	(b)FP 16
(d)FN 5	(c)TN 103

IgA EMA in children and adults
Sensitivity 98% (96 – 100), specificity 85% (78 – 91), PPV 89% (84 – 94), NPV 97% (94 – 100), efficiency 98%, +LHR = 6, -LHR = 0.02

(a)TP 146	(b)FP 18
(d)FN 3	(c)TN 101

Combinations Tests: 'test combinations containing only IgA antibodies were not considered; they are unsuitable for diagnostic purposes, because of the possibility that some patients may be deficient in IgA'.

**NB: sensitivity and specificity presented here were calculated from raw data values. These differ from the sensitivity and specificity results presented in the paper. The paper presents 'non-classified' data, which relates to the number of patients per test combination that were unable to be classified due to inconsistency between two or more tests (i.e. positive result on one test and negative result in another test(s)). This 'non-classifiable' data was incorporated into the 2x2 tables presented here as false negative data, as it is assumed that the 'non-classified' data was classed as a negative.

Combination of two tests:

IgG DGP + IgA tTG in children and adults
Sensitivity 72% (65 – 80), specificity 96% (92 – 99), PPV 96% (92 – 99), NPV 71% (64 – 79)

(a)TP 108	(b)FP 5
(d)FN 41	(c)TN 114

IgG DGP + EMA in children and adults
Sensitivity 73% (66-80), specificity 95% (91 – 98), PPV 95% (90 – 99), NPV 74% (67-81)

(a)TP 109	(b)FP 6

(d)FN 40	(c)TN 113

IgA DGP + IgG DGP in children and adults
Sensitivity 65% (57 – 72), specificity 99% (98 – 100), PPV 99% (97 – 100), NPV 69% (62 – 76)

(a)TP 97	(b)FP 1
(d)FN 52	(c)TN 118

Combination of three tests:

IgA DGP + IgG DGP + IgA tTG in children and adults
Sensitivity 73% (66-80) specificity 99% (98 – 100), PPV 99% (97 – 100), NPV 75% (68 – 81)

(a)TP 109	(b)FP 1	

(d)FN 40	(c)TN 118	
149	119	

IgA DGP + IgG DGP + EMA in children and adults
Sensitivity 58% (50 – 66), specificity 99 (98 – 100), PPV 99% (96 – 100), NPV 65% (58 – 72)

(a)TP 86	(b)FP 1	
(d)FN 63	(c)TN 118	
149	119	

IgG DGP + EMA + IgA tTG
Sensitivity 70% (62 – 77), specificity 96% (92 – 99), PPV 95% (91 – 99), NPV 73% (66-79)

(a)TP 104	(b)FP 5	

(d)FN 45	(c)TN 114	
149	119	

Combination of 4 tests:
IgG DGP + IgA DGP + EMA + IgA tTG
Sensitivity 56% (48 – 64), specificity 99% (98 – 100), PPV 99% (97 – 100), NPV 64% (58 – 71)

(a)TP 84	(b)FP 1	
(d)FN 65	(c)TN 118	
149	119	

Bibliographic reference	**Clouzeau-Girard (2011): HLA-DQ genotyping combined with serological markers for the diagnosis of celiac disease: Is intestinal biopsy still mandatory?** **Reference ID:**
Study type	Cohort (prospective)
Study quality	1. Could the selection of patients have introduced bias? NO – all patients were consecutively recruited for suspicion of CD

	2. Is there concern that the included patients do not match the review question? No – all patients were suspected of CD 3. Could the conduct or interpretation of the index test have introduced bias? NO – serological testing was carried out according to manufacturer recommendations 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO – genotyping and serological testing were as specified in study protocol 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – 3 biopsies were taken from the duodenum and classified according to Marsh criteria 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – target condition matches that specified in protocol 7. Could the patient flow have introduced bias? NO – all patients consecutively recruited, all received both index and reference tests **Overall risk of bias: Low** – All patients met target population as defined by protocol, had both serology and biopsy, and the index test and reference standard were appropriate to study protocol.
Number of patients	Total N = 170 children
Patient characteristics	Inclusion criteria: 170 patients who underwent serologic testing for coeliac disease and a small bowel biopsy between 2003 and 2006 to investigate chronic symptoms suggestive of CD. Exclusion: children excluded from the study if they had already begun gluten free diet, or if histological examination was inconclusive due to poor orientation of the sample, or if IgA deficiency was found. Patients were classified into two groups:

	Group 1: children with histology suggestive of CD (Marsh-Oberhuber classification 3a-c) Group 2: children with histology not suggestive of CD (histology showing partial villous atrophy but normal intraepithelial lymphocytes)
Intervention	I. HLA DQ2/8 genotyping – PCR performed with specific DQa1 and DQB1 primers. During the study this technique replaced with an allelic typing of the DQB1 gene, and when the susceptibility DQB1 alleles were identified, the DQA1 gene was studied. Both strategies were shown to provide identical results. Results given as positive or negative for the distinct predisposition alleles to determine the presence or absence of these genotypes. II. IgA EMA – determined using indirect immunofluorescence. Considered positive when IgA EMA antibodies were positive according to manufacturer's cut-off values III. IgA TTG – determined using ELISA assay. Considered positive when IgA tTG antibodies were positive according to manufacturer's cut-off values IV. Total IgA – Total IgA was determined in the serum to rule out selective IgA deficiency.
Comparison	Biopsy: two or three biopsies were obtained in the third part of the duodenum during endoscopy.
Length of follow up	
Location	France
Outcomes measures and effect size	Diagnostic accuracy of combined serology and genotyping 95% CI
Source of funding	Not stated
Comments	

82/162 (49%) considered positive for CD according to Marsh-Oberhuber classification (Marsh grade 3a-c).

8/170 excluded (4%): 2 children were already consuming a GFD; 1 child had previously been on a GFD and reintroduced gluten only 8 weeks earlier; 2 children had selective IgA deficiency; 3 children had intestinal biopsies which could not be classified because of bad orientation of the sample.

Of the 82 CD-positive children, 70 carried the DQ2 heterodimer and 6 possessed the DQ8 genotype. 5 patients carried both.

The most common diagnosis of those in the control group included: gastrooesophageal reflux (12.5%); psychological eating disorders (10%); lactose allergy

(2.25%); Iron-deficient anaemia (3.7%); helicobactor pyliori gastritis (10%); inflammatory bowel disease (3.7%); no aetiology (27%)

HLA DQ2/DQ8 genotyping in children

Sensitivity 99% (96 – 100), specificity 69% (59 – 79), PPV 76% (68 – 85), NPV 98% (95 – 100)

(a)TP 81	(b)FP 25
(d)FN 1	(c)TN 55

Combined IgA TTG / IgA EMA and HLA DQ2/DQ8 genotyping in children
Sensitivity 99% (96 – 100), specificity 96% (92 – 100), PPV 96% (92 – 100), NPV 99% (96 -100)

(a)TP 81	(b)FP 3
(d)FN 1	(c)TN 77

Bibliographic reference	**Porcelli (2011): Assessment of combination screening assay for celiac disease**
Study type	Case-control

Study quality	1. Could the selection of patients have introduced bias? Yes – unclear if CD confirmed patients were consecutively recruited. Control population consisted of disease controls with various other conditions and healthy blood donors. It is unclear how control cases were chosen 2. Is there concern that the included patients do not match the review question? No – all patients were confirmed of CD according to histological and serological criteria 3. Could the conduct or interpretation of the index test have introduced bias? No – assays were conducted using cut offs recommendd 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias?
Number of patients	Total N = 201 (41 CD patients and 169 control subjects)
Patient characteristics	CD patients: 41 recently diagnosed CD patients (according to histological and serological criteria), mean age 38 years. Controls: N = 169; n=145 'disease controls'; 15 with autoimmune hepatopathies; 12 with cirrhosis; 35 with viral hepatitis; 83 with other gastrointestinal diseases, and n=24 'healthy' blood donors.
Intervention	I. IgA tTG: ELISA (Quanta-Lite human recombinant tTG (h-tTG IgA). manufacturer cut-off. II. IgA Ttg: ELISA (Quanta-Lite human recombinant tTG (h-tTG IgG). manufacturer cut-off. III. IgA DGP: ELISA (Quanta-Lite gliadin IgA II). manufacturer cut-off. IV. IgG DGP: ELISA (Quanta-Lite gliadin IgG II). manufacturer cut-off. V. IgA EMA: Immunoflourescence (Eurospital). manufacturer cut-off.

	VI. IgA and IgG for tTG and DGP in a single assay (QUANTA Lite h-tTG/DGP screen ELISA assay (using purified synthetic DGP's and native human tissue transglutaminase). manufacturer cut-off.
Comparison	Biopsy-confirmed CD, or non-CD
Length of follow up	
Location	Italy
Outcomes measures and effect size	Diagnostic accuracy of serological tests 95% CI
Source of funding	
Comments	

At the time of diagnosis, all CD-confirmed patients had histological signs of Marsh 3a-c.

For the purposes of this analysis, sensitivity, specificity, PPV, and NPV values are derived from comparing CD patients to CD-negative disease controls

IgA + IgG h-tTG/DGP in adults
Sensitivity 100% (100 – 100), specificity 90 (86 – 95), PPV 75% (63 – 86), NPV 100% (100 – 100)

(a)TP	(b)FP
41	14

(d)FN 0	(c)TN 131

Bibliographic reference	**Mubarak (2011): Immunoglobin G antibodies against deamidated gliadin peptides outperform anti endomysium and tissue transglutaminase antibodies in children <2** **Reference ID:**
Study type	Cohort (prospective)
Study quality	1. Could the selection of patients have introduced bias? NO 2. Is there concern that the included patients do not match the review question? NO 3. Could the conduct or interpretation of the index test have introduced bias? NO 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO 7. Could the patient flow have introduced bias? YES – any subject with abnormal serology was biopsied **Overall risk of bias: LOW**. Study participants met protocol criteria, all underwent index tests and reference standard as stipulated by protocol , reference standard could not have introduced bias, and patient flow was unbiased. However, only participants with abnormal serology was biopsied, which may bias the outcome of establishing accuracy of serology.
Number of patients	N= 212 children suspected of CD ; <2 yrs n=41. Age range 0.6mnts – 17.8 yrs, mean age = 6.3 yrs.
Patient characteristics	Inclusion: Children <2 suspected of having CD in whom both a small intestine biopsy had been done and serological testing (EMA and/or tTGA) in the period 1998-2009. Any patient with abnormal serology, and also patients with negative serology and a high-suspicion of CD were biopsied

	All patients were on GCD, had IgA of at least 0.08 g/L, and did not suffer from giardiasis. Exclusion: none listed
Intervention	IgA DGP and IgG DGP determined using 2 methods: 1) Bindazyme Human anti gliadin EIA Kits IgA and IgG 2) Quanta Lite Gliadin IgA II and IgG II Cut-off ≥ 20 U/mL considered positive Quanta-Lite-kit combined kit used for detection of IgA and IgG-DGP, as well as IgA and IgG tTGA in human serum with a cut-off value of ≥20 U/mL Serum IgA tTGA measured by ELISA using human recombinant tTG. Cut off ≥ 10 U/mL were considered positive
Comparison	Intestinal biopsy [c] Mean of 3.2 biopsies per patient taken from distal duodenum by upper endoscopy. All biopsies revised by single pathologist . Histological diagnosis of CD made using Marsh modified classification. Marsh I and Marsh II were regarded as not conclusive for CD. Marsh III villous atrophy considered diagnostic for CD
Length of follow up	
Location	
Outcomes measures and effect size	diagnostic accuracy of serological tests 95% CI

[c] The pathologist was blinded to clinical presentation and serological results.

Source of funding	Not stated
Comments	

Total N =109/ 212 (total - 51.4%, children >2 = 83/171 Children <2 – 26/41 = 46.4%) diagnosed with CD using Marsh criteria – Marsh III lesion considered CD positive.

2 of remaining CD negative participants had a Marsh I lesion
1 of remaining CD negative participants had Marsh II lesion

PPV, NPV and all confidence intervals presented in the paper in a 2 x 2

a-DGP/tTGA children ≥2 yrs
sensitivity 98% (91-100) specificity 56% (45-66) PPV 68% (58-76) NPV 96% (85-99)

(a)TP 81	(b)FP 39
(d)FN 2	(c)TN 49

a-DGP/tTGA children < 2 yrs
Sensitivity 100% (84-100) specificity 93% (66-100) PPV 96% (79-100) NPV 100% (73-100)

(a)TP 81	(b)FP 39
(d)FN 2	(c)TN 49

Bibliographic reference	**Swallow (2013): Quality not quantity for transglutaminase antibody 2: the performance of an endomysial and tissue transglutaminase test in screening coeliac disease remains stable over time**
Study type	Cohort (retrospective)
Study quality	1. Could the selection of patients have introduced bias? NO – all patients were recruited for suspicion of CD 2. Is there concern that the included patients do not match the review question? No – all patients were suspected of CD 3. Could the conduct or interpretation of the index test have introduced bias? NO – serological testing was carried out according to manufacturer recommendations 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO – genotyping and serological testing were as specified in study protocol 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – 3 biopsies were taken from the duodenum and classified according to Marsh criteria 6. Is there concern that the target condition as defined by the reference standard does not match the

	review question? NO – target condition matches that specified in protocol 7. Could the patient flow have introduced bias? NO – authors have confirmed that all 756 participants received biopsy, IgA tTG, and IgA EMA. **Overall risk of bias: Low:** Patient selection, population, index test, comparator, and target condition all match protocol outline. It is unclear, however, if the decision to biopsy was driven by serological results, and therefore, if all patients underwent serological testing and biopsy.
Number of patients	Total N = 756
Patient characteristics	Inclusion criteria: all new patients seen between 2008 – 2009 who had been tested for tTG and EMA and had a duodenal biopsy performed. All patients were on a gluten containing diet at the time of biopsy. Exclusion criteria: Patients were excluded if only one serological test was done, or if serological testing was not carried out within 12 weeks of biopsy. Patients being monitored for pre-existing coeliac disease were also excluded from the audit.
Intervention	I. IgA tTG – ELISA test (AUESKULISA). Results interpreted as negative if < 15 U/ml, equivocal 15-5- U/ml, or positive <50 U/ml. All units are arbitrary and ssay-specific; there is no international standard to ensure comparability between assays . 2 levels of internal quality control material (IQC) with equivocal and positive results and kkit controls are assayed on each run to assess the validity of the results. II. IgA EMA – assessed by indirect immunofluorescence on monkey oesophagus tissue. Interpreted as negative, weal positive, positive, or strong positive. Weak positive and negative EMA internal quality control materials and regular review of consistency of reading thresholds are used to maintain stable reporting practice and assay sensitivity over time.
Comparison	Duodenal biopsy (Marsh grade 3 taken as CD)
Length of follow up	
Location	UK
Outcomes measures and effect size	Diagnostic accuracy of serological test 95% CI
Source of funding	None declared
Comments	

23/756 (3.04%) patients positive for CD according to Marsh grade 3. (730 controls)

Marsh grades 1 -3 lesions were found in 30 patients. Results presented here are based only on Marsh 3 lesions.

Data compared for 04 – 06 data (Hopper 08 paper) and 08 – 09 data in order to examine whether data reproducible. 08 – 09 presented here, 04 – 06 data presented in Hopper paper.

2 step strategy: TtG positive OR equivocal , then EMA positive
Sensitivity 87% (65 – 97), specificity 97% (95 – 98),

(a)TP 20	(b)FP 23
(d)FN 710	(c)TN 3

2 step strategy: TtG and EMA positive
Sensitivity 83% (60 – 94), specificity 99% (98 – 99.6),

(a)TP 19	(b)FP 7

(d)FN 4	(c)TN 726

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W *et al*. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic	Cohort/case control	N=2000 Adults (≥16yrs) UK	Inclusion: consecutive adults referred for gastroscopy without a previous diagnosis of celiac disease at a single endoscopist department from January 2004 to April 2006, N=1167 (58.3%) female, mean age 55.8yrs (range 16 to 94yrs) Exclusion: known diagnosis of coeliac disease, a coagulopathy (international normalised ratio > 1.3 or platelet count of < 80), active GI bleed or a suspected carcinoma observed during the examination (group 2: patients with a known diagnosis of celiac disease on a GFD for >1yr undergoing repeat duodenal biopsies and	IgA/IgG AGA (ELISA, AESKU Diagnostics)(cut-off > 15 U/mL) IgA tTG (ELISA, AESKU Diagnostics)(cut-off > 15 U/mL) IgA EMA (immunofluorescence, primate oesophagus)	Policy of 4 duodenal biopsy specimens from the second part of the duodenum		Marsh criteria Those with villous atrophy with supporting signs and symptoms were considered to have coeliac disease Those with villous atrophy (confirmed on a second review of the sample to ensure a well-oriented sample) and a antibody –	Not stated

analysis. *Clinical Gastroenterology & Hepatology* 2008;**6**:314-20			serologic analysis – results not included in this table)	Total IgA (Behring BN2 nephelometer, Siemens) Blood for serological tests taken at the same time as the biopsy			ve profile were classed as seronegative coeliac disease, to confirm this they were required to have DQ2 or DQ* pattern consistent with CD and a clinical and histological response to a GFD	
Effect size: (CI 95%) N=77/1000 diagnosed with coeliac disease (prevalence, all patients attending for gastroscopy of 3.9%); N=29 Marsh 3a, N=30 Marsh 3b, 18 Marsh 3c lesions IgA deficiency 0.7% (N=14/2000) Symptoms (coeliac disease vs. non coeliac disease): Weight loss (15.6% vs. 5.3%), p<0.05 Diarrhoea (42.9% vs. 5.2%), p<0.05 Dyspepsia (17.3% vs. 1%), p<0.05								

Reflux (13.8% vs 1%), p<0.05

Dysphagia (7.2% vs. 0%), p<0.05

Those with coeliac disease were significantly younger (mean age 48.0 vs. 56.1 yrs), p<0.05, there were significantly more females (70.1% vs. 57.9%), p<0.05, than those without coeliac disease

IgA tTG

sensitivity 90.9% (82.4 to 94.5), specificity 90.9% (89.5 to 92.1), PPV 28.6% (23.3 to 34.5), NPV 99.6% (99.2 to 99.8)

2X2:

(a) TP 70	(b) FP 175
(c) FN 7	(d) TN 1748

IgA EMA

sensitivity 87.0% (77.7 to 92.8), specificity 98.0% (97.4 to 98.6), PPV 64.4% (54.9 to 73.0), NPV 99.4% (99.0 to 99.7)

2X2:

(a) TP 67	(b) FP 37
(c) FN 10	(d) TN 1886

If tTG +ve and then EMA +ve (2-step)

sensitivity 85.7% (76.2 to 91.8), specificity 98.6% (98.0 to 99.0), PPV 71.7% (61.8 to 79.9), NPV 99.4% (99.4 to 99.0)

2X2:

(a) TP 66	(b) FP 26
(c) FN 11	(d) TN 1897

Both tTG +ve and EMA +ve

sensitivity 85.7% (76.2 to 91.8), specificity 98.6% (98.0 to 99.0), PPV 71.7% (61.8 to 79.9), NPV 99.4% (99.4 to 99.0)

2X2:

(a) TP 66	(b) FP 26
(c) FN 11	(d) TN 1897

Either tTG +ve or EMA +ve

sensitivity 92.2% (84.0 to 96.4), specificity 90.3% (88.9 to 91.6), PPV 27.6% (22.5 to 33.4), NPV 99.7% (99.3 to 99.8)

2X2:

(a) TP 71	(b) FP 186
(c) FN 6	(d) TN 1737

IgG AGA

sensitivity 48.1% (37.3 to 59.0), specificity 95.8% (94.9 to 99.6), PPV 31.6% (23.9 to 40.5), NPV 97.9% (97.1 to 98.4)

2X2:

(a) TP 37	(b) FP 77
(c) FN 40	(d) TN 1849

IgA AGA

sensitivity 49.4% (38.5 to 60.2), specificity 89.6% (88.2 to 90.1), PPV 16.0% (11.9 to 21.2), NPV 97.8% (97.0 to 98.4)

2X2:

(a) TP 38	(b) FP 200
(c) FN 39	(d) TN 1723

Both IgA and IgG AGA

sensitivity 36.4% (26.5 to 47.5), specificity 98.8% (98.2 to 99.2), PPV 54.9% (41.4 to 67.7), NPV 97.4% (96.7 to 98.1)

2X2:

(a) TP 28	(b) FP 23
(c) FN 49	(d) TN 1900

Using only IgA tTG +ve 245 would have undergone biopsy and 1 in 11 cases of coeliac disease would have been missed

Using only IgA EMA +ve 104 would have undergone biopsy and 1 in 8 cases of coeliac disease would have been missed

Using IgA tTG +ve and then IgA EMA +ve 92 would have undergone biopsy and 1 in 7 cases of coeliac disease would have been missed

Using either IgA tTG +ve or IgA EMA +ve 257 would have undergone biopsy and 1 in 13 cases of coeliac disease would have been missed

Those with partial villous atrophy (Marsh 3a or 3b) had significantly lower mean tTG titre (168.1 U/mL and 165.0 U/mL) than those with total villous atrophy (255 U/mL), $p<0.05$

Those with Marsh 1 or 2 had significantly lower mean tTG titre (27.7 U/mL and 23.0 U/mL) than those with villous atrophy, $p<0.05$

EMA sensitivity 79% in partial atrophy, 100% in total atrophy, p<0.01

tTG sensitivity 86.0% (Marsh 3a), 100% (Marsh 3c), p<0.05

QUADAS:

1. Could the selection of patients have introduced bias? NO - All patients were consecutively recruited
2. Is there concern that the included patients do not match the review question? NO – patients matched review protocol
3. Could the conduct or interpretation of the index test have introduced bias? NO – manufacturer test cut-off used.
4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO
5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – reference standard matched review protocol
6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – target condition matched review protocol
7. Could the patient flow have introduced bias? NO – all patients received same reference standard and were included in analyses in accordance with review protocol

Overall risk of bias: LOW – Patients Were consecutively recruited. Index and reference tests, and target condition matched review protocol. All participants received the same reference standard and index tests.

D.6 Review question 5.3

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if a consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? YES – 24 were excluded but explanation not given
Number of patients	53
Patient characteristics	Inclusion criteria: Presence of villous atrophy and positive IgA EMA Exclusion criteria: IgA deficiency, Non-compliance with diet or biopsy Age at diagnosis – mean (range): 51 years (16 – 81 years) Gender (M/F): 14/39 Immunoglobulin A (IgA) deficiency: None Time on gluten-free diet – mean (range) : 12 months Assessed by: Dietitian for adherence
Intervention	IgA EMA by indirect immunofluorescence using primate oesophagus (Biodiagnostics, Upto-upon-Severn, England) with a titer of ≥ 1.5 as cut-off Duodenal biopsy Dietitian assessment
Comparison	NA

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
Length of follow up	12 months
Location	Northern Ireland
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms 48/53 (90.6%) IgA EMA – number testing negative At 3 months = 13/53 (58% At 6 months = 50/53 (75%) At 9 months = not reported At 12 months = 46/53 (87%) Duodenal biopsy TVA/STVA at baseline (n = 41) At 12 months = 13 were normal, 18 had PVA and 10 were non-responders (persistent TVA/STVA) PVA at baseline (n = 12): At 12 months = 7 were normal, 1 was Marsh grade 1 and 4 were non-responders (persistent PVA) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence 5/53 (9.4%) reported as non-adherent

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Impact on carers Not reported Health-related quality of life Not reported
Source of funding	None reported
Comments	All responders were adherent to GFD, non-responders were non-adherent Of 79 candidates for inclusion, 2 were EMA negative at baseline due to IgA deficiency, and 62 test EMA positive at baseline, 9 did not have a full 12 months of GFD, only 53 EMA + at baseline were followed up Study did not report on agreement or correlation between serology and biopsy
Bibliographic reference	**Autoimmunity** **2007 40 (2) PAGES 117-121** **Two-year follow-up of anti-transglutaminase autoantibodies among celiac children on gluten-free diet: comparison of IgG and IgA** **Martin-Pagola, Ainhoa, Ortiz-Paranza, Lourdeset al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? YES – unclear if a consecutive sample was used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	93
Patient characteristics	Inclusion criteria: ESPGHAM diagnosis of CD with HLA-DRB! Typing and GFD adherent Exclusion criteria: Non-adherence to GFD Age at diagnosis – mean (range): 3.56 years (0.94 – 17.5) Gender (M/F): 35/58 (62.4% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – mean (range): 2 years Assessed by: Not reported
Intervention	IgA anti-tTG IgG anti-tTG Both determined by immunoprecipitation radioassays. S25 labeled human recombinant tTGase was incubated with 3µl of serum at 4oC overnight and immune complexes were precipitated with a 25% (v/V) suspension of protein-A agarose (Amersham Biosciences, Barcelona, Spain) for IgG or a 20% (v/v) suspension of agarose-conjugated IgA specific antibodies (Sigma cat. No. A2691) St Louis, MO) for IgA. Cut-off values were set as the sum of the mean and 3/SD of the index values of 50 serum samples from the general population.
Comparison	NA
Length of follow up	24 months
Location	Spain
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms (reported as remission)

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Not reported Response – defined as number of people testing negative on serology At 6 months IgA: 46/93 (49%) IgG: 59/93 (63%) At 24 months IgA: 82/93 (88%) IgG: 90/93 (96%) Biopsy – response = normal biopsy N = 41* Of those with Marsh 3a or 3b at diagnosis 4 (9%) were Marsh 2 12 (30%) were Marsh 1 25 (61%) were Marsh 0 Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Impact on carers Not reported Health-related quality of life Not reported
Source of funding	Funded by the Spanish Ministry of Health
Comments	Only 41 consented to a second biopsy after 2 year GFD Only those with elevated serology titers at baseline followed up Study did not report on agreement or correlation between serology and biopsy
Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? NO Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. Yes – unclear of exact timing of tests Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Could the patient flow have introduced bias? NO
Number of patients	20
Patient characteristics	Inclusion criteria: Diagnosed with CD with March 3 criteria Exclusion criteria: IgA deficiency Age at diagnosis – median (range): 62 years (29 – 86 years) Gender (M/F): 10/12 (54.5% female) Immunoglobulin A (IgA) deficiency: NA Time on gluten-free diet – mean (range) : 12 months Assessed by: Dietitian for adherence
Intervention	AGA (AGA was tested using UniCAP Gliadin IgA (Pharmacia Diagnostics, Uppsala, Sweden) and was defined as positive with a result >3 $mg_A\ L^{-1}$.) tTGgrh (Celikey®, tTGrh, IgA antibody assay (Pharmacia Diagnostics, Freiburg, Germany). It was defined by the producer as positive when >8 U mL^{-1}, negative when <5 U mL^{-1}, borderline between 5 and 8 U mL^{-1}) tTGgp (ImmuLisa®, tTGgp with guinea-pig-derived tTG (IMMCO, Buffalo, NY, USA). The result was defined by the producer as positive when >25 U, negative when <20 U, borderline when 20–25 U) IgA EMA (indirect immunofluoflourescence using monkey oesophageal tissue. Tissue sections from marmoset monkey oesophagus were mounted on microscopic slides. Undiluted sera and sera diluted 1 : 25 with phosphate-buffered saline (PBS) was applied to slides, which were incubated for 30 min at room temperature. After washing with PBS the sections were covered with fluorescein conjugated rabbit-antihuman IgA (Dako, Copenhagen, Denmark) for 30 min, washed with PBS and examined by fluorescence microscopy. Positive sera were further diluted (1 : 5, 1 : 10, 1 : 25, 1 : 100, 1 : 400 and 1 : 1600). Sera positive in dilution 1 : 10 or more were defined as positive

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Biopsy (Three to four biopsy specimens were obtained during upper endoscopic examination of each patient from the lower part of the duodenum descendens with standard forceps. All biopsies were fixed in a 4% buffered formaldehyde solution. Fixation, embedding and cutting were carried out according to routine methods)
Comparison	NA
Length of follow up	12 months
Location	Sweden
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms (reported as remission) 16/18 (88.9%) Response – defined as number of people testing negative on serology <u>AGA IgA</u> at 3 months =9/114 (74%) at 6 months = 14/15 (93%) at 9 months = not reported at 12 months = 15/15 (100%) <u>IgA EMA</u> at 3 months =7/17 (41%) at 6 months = 13/17 (65%) at 9 months = not reported at 12 months = 14/16 (87%) <u>IgA tTGrh</u> at 3 months = 8/14 (57%)

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	at 6 months = 10/14 (71%) at 9 months = not reported at 12 months = 14/14 (100%) Biopsy – response = normal biopsy At 12 months = 16/18 (88.9%) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Not reported Health-related quality of life Not reported
Source of funding	Authors are research staff at Pharmacia Diagnostic manufacturers for some of the testing kits but they state no financial support was received.
Comments	1 person excluded for IgA deficiency and 1 not included in results as they stopped the GFD 2 participants did not have a repeat biopsy at 12 months,

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Both non-responders at 12 months were in remission at follow-up biopsy but no timeframe reported Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
Study type	Cohort (Prospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	30
Patient characteristics	Inclusion criteria: Diagnosis of CD according to EPSGHAN criteria

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
	Exclusion criteria: None reported Age at diagnosis – mean (range): 6 (1 – 24 years) Gender (M/F): 13/17 (56.7% female) Immunoglobulin A (IgA) deficiency: 3/30 (10%) Time on gluten-free diet – mean (range) : 12 months Assessed by: Not reported
Intervention	IgA EMA Ig ARA
Comparison	NA
Length of follow up	12 months
Location	Greece
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Response – defined as the number of people testing negative on serology <u>IgA EMA</u> At 3 months = 17/30 (57%) At 6 months = 25/30 (83%) At 9 months = 17/30 (90%) At 12 months = 30/30 (100%) <u>Ig ARA</u> At 3 months = 23/30 (77%) At 6 months = 26/30 (87%)

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
	At 9 months = 30/30 (100%) At 12 months = 30/30 (100%) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Health-related quality of life Not reported
Source of funding	None reported
Comments	This study reports that ‘as the half-life of IgA is shorter than that of IgG, the IgA antibodies respond more rapidly to gluten changes in the diet and, therefore, are more appropriate for the follow-up of CD patients” IgA AGA and IgG AGA examined with home-made kits also studied so data were not used in this review Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**
Study type	Cohort (prospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if a consecutive ample used Is there concern that the included patients do not match the review question? UNCEAR – age group not reported Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	50
Patient characteristics	Inclusion criteria: Diagnosis of CD based on the presence of flattened intestinal villi on duodenal biopsy. Exclusion criteria: None reported Age at diagnosis – mean (sd): mean not reported range 6 – 11 years Gender (M/F): 17/33 (67% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – 24 months
Intervention	.IgA tTG
Comparison	NA
Length of follow up	24 months
Location	Romania
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**
	number of people with negative test results <u>IgA tTG</u> at 3 months = 34/50 (68%) at 6 months = 34/50 (68%) at 9 months – not reported at 12 months = 41/50 (82%) at 24 months = 40/50 (80%) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Not reported Health-related quality of life Not reported
Source of funding	The authors report no conflicts of interest.
Comments	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
Study type	Cohort (Retrospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR not reported if a consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	70
Patient characteristics	Inclusion criteria: Newly diagnosed with CD Exclusion criteria: None reported Age at diagnosis – mean (sd): 39 years (11.1) Gender (M/F): 20/50 (71.4% female) Immunoglobulin A (IgA) deficiency: 0/70 (0%) Time on gluten-free diet – 36 months

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
	Assessed by: Not reported
Intervention	Anti-endomysium (EmA) which were determined semiquantitative by the technique of indirect immunofluorescence (IIF) using a commercial kit INOVA (NOVA Lite Monkey Oesophagus IFA Kit/Slides, USA) on a 5-μm-thin cryostat section of distal monkey oesophagus as antigen substrate. Patient samples were tested in dilutions ranging from 1 : 5 to 1 : 2560. The antibody titre was defined as the highest sample dilution yielding fluorescence. Titre below1 : 5 was considered negative. Anti-tissue transglutaminase class IgA (tTG-A) which were assayed using a commercial anti-tTG type IgA ELISA test kit (QUANTA LiteTM, INOVA Diagnostics, USA). The cut-off value provided was 25U. ELISA was performed in duplicate according to the manufacturer's instruction.
Comparison	NA
Length of follow up	36 months
Location	Greece
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Response reported as number of people testing negative serology among those who were strictly compliant <u>IgA EMA</u> At 6 months = 20/51 (39.2%) At 12 months = 37/51 (72.5%) At 36 months = 48/51 (94.1%) <u>IgA tTG</u> At 6 months = 10/51 (19.6%)

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
	At 12 months = 25/51 (49.0%) At 36 months = 41/51 (80.4%) Complications of coeliac disease Not reported Dietary adherence 19 were considered partially adherent while 51 were considered strictly adherent Impact on carers Not reported Health-related quality of life Not reported
Source of funding	No funding reported but conflicts of interest listed
Comments	Unable to calculate data for accuracy of detecting non-adherence Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
Study type	Cohort (prospective)
Study quality	Could the selection of patients have introduced bias? NO Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	101
Patient characteristics	Inclusion criteria: CD confirmed buy biopsy (Marsh 2 or March 3) and positive clinical response to GFD Exclusion criteria: None reported Age at diagnosis – median (range): 37 years (21 – 72) Gender (M/F): 22/79 (78.1% female) Immunoglobulin A (IgA) deficiency: (%) Time on gluten-free diet – 12 months Assessed by: Not reported
Intervention	Serum EmAs were detected by immunofluorescence, using commercial slides of monkey esophagus (The Binding Site Ltd., distributed by Alfa Biotech). Sera were tested, as indicated by the manufacturer, at a 1:10 initial dilution, with the inclusion of positive and negative controls in every batch of tests. CD EmA-negative sera were further tested at a 1:5 dilution, and no false-negative results were obtained. Used four commercially available sandwich ELISAs that use human recombinant antigen (h-tTG): h-tTG 1 (DRG Diagnostics, distributed by Pantec S.r.l.); h-tTG 2 (EU-tTG® IgA; Eurospital S.p.A); h-tTG 3 (Immunodiagnostik, distributed by Li StarFISH); and h-tTG 4 (CELIKEYTM; Pharmacia & Upjohn, which uses human recombinant antigen extracted from eukaryotic cells. The

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
	same evaluation was also carried out with a sandwich ELISA that uses guinea pig tTG antigen (gp-tTG; GENESIS Diagnostics, distributed by Pantec S.r.l Duodenal biopsy
Comparison	NA
Length of follow up	12 months
Location	Italy
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Response reported as number of people normal duodenal biopsy at 12 months Normal (mucosal recovery) = 12/101 (12%) Improvement (Marsh grade I) = 51/101 (50%) no change (Marsh grade II or III) = 38/101 (38%) Complications of coeliac disease Not reported Dietary adherence NA Impact on carers Not reported

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
	Health-related quality of life Not reported
Source of funding	None reported
Comments	Mean percentage changes in anti-tTG values were 81% (range, 75–86%) for h-tTG 1, 51% (range, 43–60%) for h-tTG 2, 51% (range, 42–61%) for h-tTG 3, 77% (range, 69–85%) for h-tTG 4, and 75% (range, 67–82%) for gptTG. The concordances of the different assays in both positive (persistent histologic impairment and positive serologic markers) and negative (reconstituted mucosa and negative serologic markers) individuals vs histologic score were 29% for h-tTG 1, 65% for h-tTG 2, 14% for h-tTG 3, 16% for h-tTG 4, and 19% for gp-tTG, compared with 48% for EmA testing.

Bibliographic reference	**Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet** **Reference ID:**
Study type and aim	Prospective cohort study to establish aetiology of continued symptoms on a gluten-free diet (GFD)
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias?

Bibliographic reference	Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet Reference ID:
	Overall risk of bias:
Number of patients	Total N = 112
location	England
Patient characteristics	**Inclusion criteria:** Patients prospectively recruited who were referred with a diagnosis of non-responsive coeliac disease (NRCD) between 2002 and 2003. All patients had continued symptoms on a gluten free diet **Exclusion criteria**: none listed **Mean age**: 48.5 **Mean age at diagnosis**: 31 years **Mean years since diagnosis**: 3 years (1 – 12 years)
Signs and symptoms	Lethargy 43% Diarrhoea 65% Abdominal pain 37% Weight loss 23% Nausea and vomiting 10% Anemia 10% 2 symptoms = 49% 3 symptoms 20%
Investigations	Appraisal of CD diagnosis, history of symptoms, clinical exam, routine blood tests and assessment of diet and GFD compliance. 'Patients were then investigated according to usual clinical practice and subsequent findings'. Those who developed further symptoms were reinvestigated. Unless an obvious cause was immediately apparent, a further bowel biopsy was undertaken. Jumbo endoscopy forceps were used to obtain four samples that were carefully placed, mucosal surface upwards.
Length of follow up	All patients followed for a minimum of 2 years

Bibliographic reference	**Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet** **Reference ID:**
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 12/112 (11%) • Gluten ingestion: 45/100 (45%) • Microscopic colitis: 11/100 (11%) • Bacterial overgrowth: 9/100 (9%) • Lactose intolerance: 7/100 (7%) • Inflammatory colitis 7/100 (7%) • IBS: 10/100 (10%) • RCD 9/100 (9%) Other causes: (all 1 - 2 %) • Anorexia • Pancreatic insufficiency • Diverticular disease • Medication-induced diahorrea • Combined variable immunodeficiency • Colorectal cancer • Anorectal dysfunction • Human immunodeficiency virus
Source of funding	Not stated
Comments	
Definition of NRCD: Failure of expected symptomatic response to GFD Total N CD = 100 (after removal of 12 non-CD)	

Bibliographic reference	Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet Reference ID:
After 2 years 78% reported being symptom-free	

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
Study type and aim	Cohort (retrospective) study to determine etiologies of NRCD
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N = 113 consecutive patients identified as NRCD from a pool of 603 biopsy-confirmed CD patient
location	US
Patient characteristics	• **Inclusion criteria**: a database of all patients diagnosed with biopsy-proven CD between 2000 and 2006 was examined for cases of NRCD and RCD defined by criteria listed below. For analyses, RCD cases were grouped with ulcerative jejunitis (UJ) and enteropathy associated T-cell lymphoma (EATL). • **Exclusion criteria**: Individuals without definitive evidence of CD in the form of duodenal biopsy exam, or a skin biopsy in case of dermatitis herpetiformis were not included • **Mean age**: NA • **Mean age at diagnosis**: 42 years

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
	• **Mean years since diagnosis**: NA • **Mean duration of symptoms**: NA
Signs and symptoms	• Diarrhoea: 54% • Lethargy: 5% • Abdominal pain: 55% • Weight loss : 20% • Nausea and vomiting : NA • Anaemia: NA
Investigations	Clinical notes, lab data, and diagnostic tests performed were investigated for each individual patient to identify evidence of NRCD. All entries were reviewed twice for accuracy Patients believed to be at high risk were evaluated for T-cell clonality and aberrant T-cell markers.
Length of follow up	Mean follow up = 20 months (2 – 126 months)
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 14/113 (12%) • Gluten ingestion: 36% • Microscopic colitis: 6% • Bacterial overgrowth (SIBO): 6% • Lactose intolerance: 8% • Inflammatory colitis:NA • IBS: 22% • RCD: 10% Other causes:

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
	• Eating disorder • Peptic ulcer disease • Gastroparesis • Crohn's disease • Fod allergy • CVID • Duodenal adenoma
Source of funding	Not Stated
Comments	
Diagnostic criteria for NRCD: referral for evaluation of lack of response to a gluten free diet. Failure of clinical symptoms or lab abnormalities typical of CD to improve within 6 months after GFD. Recurrence of symptoms and/or lab abnormalities typical of CD while on GFD. Refractory CD definition: persistence of villous atrophy despite strict GFD and no evidence of another pathology, including overt lymphoma	

Bibliographic reference	Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach Reference ID:
Study type and aim	Cohort (retrospective) study to identify causes of persistent symptoms in patients with NRCD and characterise patients with RCD
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias?

Bibliographic reference	**Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach** **Reference ID:**
	Overall risk of bias:
Number of patients	Total N = 55
location	US
Patient characteristics	• **Inclusion criteria**: patients who had been evaluated for NRCD between 1997 and 2001. Included in the study when a definite diagnosis of CD was secured based on the clinical picture, on biopsy findings compatible with CD, and on criteria met for diagnosis of NRCD or RCD (listed below). • **Exclusion criteria**: Patients excluded if the CD diagnosis was reversed based on absence of CD on biopsy and presence of other disease responsible for their symptoms • **Mean age NRCD**: 51.3 (21-80) • **Mean age RCD:** 66.1 (56-82) • **Mean age at diagnosis**: • **Mean years since diagnosis**:
Signs and symptoms	• Diarrhoea: 84% • Lethargy:37% • Abdominal pain: 52% • Weight loss :47% • Nausea and vomiting : 17% and 10%, respectively • Anaemia: 37%
Investigations	Patient records and small bowel biopsy results were reviewed. Patients underwent a systematic sequential evaluation including: • detailed dietary review, • serological testing for CD • repeat small intestinal and

Bibliographic reference	**Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach** **Reference ID:**
	• colonic biopsy, • small bowel aspirates for quantitative culture, • 72 hr stool fat measurement • small bowel radiographic studies • CT body imaging. All tests were not done in patients if an obvious case of symptoms was found which resulted in resolution of symptoms Dietary assessment involved 3 steps: 1. Physician review and direct questioning regarding patient's perspective of GFD 2. Direct and detailed evaluation by a dietician expert in celiac disease and the GFD 3. Serological tests, primarily endomysial antibodies (EMA) and gliadin antibodies (AGA)
Length of follow up	
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 6/55 (11%) (49 patients with CD) • Gluten ingestion: 25/49 (51%) • Microscopic colitis: 5/49 (10%) • Bacterial overgrowth: 7/49 (14%) • Lactose intolerance :NA • Inflammatory colitis :NA • IBS: 4/49 (8%) • RCD: 9/49: (18%) Other causes: • Pancreatic insufficiency 6/49 • Protein losing enteropathy

Bibliographic reference	**Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach** **Reference ID:**
	True RCD cases- further investigations: • T-cell receptor gene rearrangement: 6/9 tested for T-cell receptor gene rearrangement – 2/6 positive • Bone mineral density: 7/9 measured. 6/7 (85%) had osteoporosis. Prevalence of osteoporosis in RCD significantly higher than NRCD (10/28, 35%).
Source of funding	
Comments	
NRCD definition: persistence or recurrence of symptoms for up to 12 months, despite presumed GFD RCD: defined as persistence of symptoms and evidence for histological injury despite adhering to GFD for up to 12 months When original diagnosis of CD not made in authors institution (49 cases), original biopsy slides were retrieved if possible/ 32 original specimens retrieved and reviewed by same GI pathologist. Diagnosis in remaining cases based on original biopsy report, repeat biopsy, serological markers for CD, and response to GFD. Of those without CD, diagnosis was IBS (2/6), protein losing enteropathy (1/6|), malrotation of the gut (1/6), wheat allergy (1/6) Whipple disease (1/6).	

Bibliographic reference	**Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae** **Refernce ID:**
Study type and aim	Prospective cohort study to assess value of double-balloon enteroscopy in patients with RCD
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias?

Bibliographic reference	Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae Refernce ID:
	6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N = 21
location	Netherlands
Patient characteristics	**Inclusion criteria:** consecutive patients referred to specialist centre for DBE between 2004 and 2005 all patients were symptomatic on a strict GFD for a median period of 60 months and were suffering from persistent villous atrophy on duodenal histology. **Exclusion criteria**: None listed **Mean age**: 61 (41-89) **Mean age at diagnosis**: NA **Mean years since diagnosis**:5 (0.3 – 33)
Signs and symptoms	17/21 were symptomatic: Lethargy NA Diarrhea 11/21 (52%) Abdominal pain 3/21 (14%) Weight loss 3/21 (14%) Nausea and vomiting NA Anemia NA
Investigations	Primary: Double balloon enteroscopy (DBE) o Done within 4-6 weeks of initial duodenoscopy o Endoscope and flexible overtube both provided with soft latex balloons connected through built-in air route to a

Bibliographic reference	Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae Refernce ID:
	controlled pump system. ○ Advancement or withdrawal of scope achieved by deflating or inflating balloons ○ Endoscope introduced orally in all patients ○ Length of visualized small bowel was estimated by calculating su of each sequential progressive extension of the scope through overtue ○ Patients prepared with Klean Prep bowel cleanse ○ Midazolam mean dose 10mg and mean dose 7.5 µg of fentanyl for conscious sedation ○ Small bowel assessed for a-priori defined low risk: reduction (≤ 3 per endoscopic field of view) or loss of folds, scalloping, nodularity or muscosa or mosaicism, visible vessels, after air insufflation. ○ Ulcerations at ;eat 5mm in diameter and stenosis were considered high risk lesions for their potential risk of harbouring malignancy ○ Endoscopic findings considered jejunal if were found in proximal 2-3 m of the calculated endoscopic insertion depth ○ Small bowel as visualized by DBE divided into proximal, distal, and middle, and 4 biopsies taken from each segment. Diagnostic workup prior to DBE: • IgA tTTG, IgA EMA CD antibodies • HLA DQ2/DQ8 genotyping • Eosophagogastroduodenoscopy • Abdominal CT (n=14) • Video capsule endoscopy (n=7)
Length of follow up	Median interval of 36 months
Outcome	Utility of DBE in examination of patients with RCD
Results	DBE findings: Jejunal ulcerations which revealed presence of EATL found in 5/21 (24%) of patients (95% CI: 10-45%) Ulcerative lesions in absence of histological evidence of EATL found in another 2 patients (9%; 95% CI: 2-28%). – histology of nonulcerative mucosa classified as Marsh 3 and therefore were considered to have ulcerative jejunitis In remaining 14 patients (66%), low risk features i.e. flattened villi, loss of folds, scalloping, and nodularity were

Bibliographic reference	Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae Refernce ID:
	found by double balloon enteroscopy – these patients diagnosied wih RCD on basis of persistent villous atrophy despite GFD Esophagogastroduodenoscopy findings: Could detect low-risk lesions in duodenum Did not detect EATL nor ulcerative jejunitis in any patient CT findings: Abnormal in 4 patients with EATL Missed diagnosis of EATL in 1 patient Missed both ulcerative jejunitis patients Presence of EATL further suggested in 4/7 patients who had CT – after median 36month follow-up none of these patients developed lymphoma Author conclusions: complications of RCD like EATL and UJ can be efficiently detected or excluded by DBE
Source of funding	
Comments	
Duodenal and small bowel biopsies evaluated according to Marsh criteria Diagnosis of EATL: Established according to WHO classification based o histological and immunohistochemical features and TCR gene rearrangement studies. Immunohistochemical features are evidence of large or medium sized T-cell proliferation expressing CD3(+) CD8 (+-)and CD103(+) Standard esophagogastroduodenoscopy failed to diagnose 2 EATL patients due to limitations in introducing the endoscopy beyond ligament of Treitz Ulcers are more commonly located in the jejunum and ileum rather than duodenum and DBE more easily able to investigate these distal locations.	

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
Study type and aim	Retrospective cohort study to describe VCE findings in NRCD and identify VCE findings associated with poor prognosis

Bibliographic reference	**Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease** **Reference ID:**
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N = 48
location	Netherlands
Patient characteristics	**Inclusion criteria:** all adults who underwent VCE for evaluation of persisting symptoms despite GFD at specialist centre between 2005 and 2010. Patients divided into four classifications: Uncomplicated CD (n=22), RCD I (n=12), RCD II (n=11), EATL (n=3) **Exclusion criteria**: For EATL patients; patients were excluded if they had a diagnosis of primary EATL, with no diagnosis of CD prior to developing EATL. **Mean age**: • uncomplicated:49 (18.5) • RCD I: 62 (9.8) • RCD II: 63 (9.8) • EATL: 64 (1.7) **Mean age at diagnosis**: • uncomplicated:42 (18.6) • RCD I: 49 (13.4) • RCD II: 55 (15.5) • EATL: 60 (3.7)

Bibliographic reference	**Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease** **Reference ID:**
	Mean years since diagnosis: NA
Signs and symptoms	• Lethargy - NA • Diarrhea – 24/48 (50%) • Abdominal pain – 8/48 (17%) • Weight loss – 12/48 (25%) • Nausea and vomiting - NA • Anemia - 2/48 (4%)

Investigations	• VCE
	  ○ Performed only in absence of signs suggestive of small-intestinal stenosis
	  ○ 2L polyethylene glycol bowel preparation
	  ○ Small intestine divided into proximal (first ¼) and a distal part (remaining ¾) based on small-bowel transit time (SBTT)
	  ○ When small bowel exam incomplete, used transit data from complete studies and defined proximal small intestine as part of visualized within 2 SD of mean ¼ of the SBBT of complete studies
	  ○ Proximal and distal part of all VCE studies were reviewed for signs derived from previous publications on VCE or conventional endoscopy in CD, inc:
	  ▪ Villous atrophy
	  ▪ Mosaic pattern
	  ▪ Scalloping of folds
	  ▪ Mucosal fissures
	  ▪ Erosions
	  ▪ Ulcers
	  ▪ Strictures
	  ▪ Masses
	  ○ Size of erosion and ulcers classified arbitrary as either small (≤5mm), intermediate (5-10 mm), or large

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:

	(>10mm).
	• Small bowel biopsy
	  ○ Obtained during esophagogastroduodenoscopy and/or DBE within 2 months of VCE
	  ○ Graded according to Marsh classification
	• T-cell flowcytometry
	
	• Double-balloon endoscopy

Length of follow up	For Uncomplicated and RCD patients, mean follow up 25 months. For EATL patients, 2 months.
Outcome	VCE, flowcytometry, findings in uncomplicated, RCD and EATL patients
Results	Other causes of NRCD found in 17 patients: • Gluten ingestion: 14 • Lactose intolerance: 2 • Inflammatory colitis: 1 VCE findings: No clear relationship between size and number of erosions or ulcers and final diagnosis. 2 patients (RCD I and uncomplicated CD) diagnosed with ulcerative jejunitis Most abnormalities encountered in proximal small bowel Comparison according to prognosis: low risk (uncomplicated RCD and RCD I) vs high risk (RCD II and EATL) Presence of proximal focal erythema associated with risk of poor prognosis (i.e. diagnosis of RCD II or EATL) Absence of progression of the capsule to the distal intestine was associated with increased risk of poor prognosis (i.e. diagnosis of RCD II or EATL). No patients without these features died at follow up 2/15 (13%) patients with one of these died at follow-up 4/5 (80%) patients with both of these features died at follow-up **Author conclusion**: VCE minimally invasive endoscopic modality that could be of use in identifying patients with NRCD who

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
	require urgent and intensive medical treatment
Source of funding	
Comments	

Definitions:

Uncomplicated CD: diagnosed if during follow-up clinical symptoms, villous atrophy, and positive serology improved without need for immunosuppression, or if an alternative reason for symptoms was established

RCD: defined by persistent or recurrent malabsorbtive symptoms and villous atrophy despite strict GFDfor at least 6 months in the absence of other causes.

RCD type I: characterised by normal, polyclonal immunophenptype of IEL's with favourable response to nutritional support and immunosuppressive therapy

RCD type II: characterised by presence of intraepithelial lymphocytes immunophenotype or by differences in clonality of the T-cell receptor (TCR) gene. Abnormal phenotype (>20% of the CD 103(=)/CD45(+) IEL's lacking surface CD3 on flowcytometry).

EATL: diagnosis based on international WHO criteria. Divided into primary and secondary. Primary excluded. Secondary is when patients were known to have CD prior to EATL diagnosis

Ulcerative jejunitis: defined as presence of ≥ 3 ulcers in the jejunum during enteroscopy

Bibliographic reference	Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system Reference ID:
Study type and aim	Retrospective cohort study to determine MR enteroclysis findings in patients with uncomplicated CD, RCDI, and RCD II, and to determine diagnostic accuracy of MR enteroclysis to detect CD-related malignancies
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question?

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
	5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N=68
location	Netherlands
Patient characteristics	**Inclusion criteria:** From VU hospital MR database, authors identified 80 MR enteroclysis studies that were obtained between 2004 and 2009 in 72 patients who experienced symptoms despite being on a GFD. Consecutive studies obtained from Sept 2004 – Dec 2005 were included in the test group and used to construct a scoring system to predict RCD II. Consecutive studies obtained from January 2006 – July 2009 were included in the validation group and used to validate the scoring system. • Test group – n=28 • Validation group - n=40 **Exclusion criteria**: follow-up studies (n=12) obtained after chemotherapy and/or autologous hematopoietic stem cell transplantation for RCD or enteropathy-associated T-cell lymphoma were excluded **Mean age**: 56 (18-81) **Mean age at diagnosis**: NA **Mean years since diagnosis:** NA:
Signs and symptoms	Lethargy - NA Diarrhea – 5/68 (7%) Abdominal pain – 21/68 (31%) Weight loss – 34/68 (50%) Nausea and vomiting – 3/68 (4%) Anemia - NA

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**

Investigations	MR enteroclysis
	• Overnight fast, 9-F nasojejunal tube positioned distal to duodenojejunal junction with fluoroscopic guidance
	• During MR imaging, a minimum of 2000mL of 0.5% methylce3llulose solution in water was infused through the tube, at a flow rate of 80-100mL/min using MR compatible pump system. No IV contrast used
	• Imaging ceased when optimal distension of the full small bowel and cecum was obtained
	• No antispadmodics administered
	• Number of jejunal folds and ileal folds per 5cm calculated by using maximum value of three measurements for each loop
	• Small bowl thickening was considered to be present when the wall thickness of a distended small-bowel loop was more than 3mm
	• Itaussception defined as a target mass or a complex layered mass within the bowl luman
	• Lymph nodes larger than 1cm in diameter in their shortest axis considered enlarged
	• Mesenteric fat infiltration defined as decrease in signal intensity of mesentry surrounding mesenteric vessels
	Study Pipeline:
	• Test group (n=28)
	  ○ Patients grouped into uncomplicated CD; RCD I or RCD II (see diagnostic criteria below)
	  ○ Comparison of diagnostic groups – NB this is exploratory only, no corrections for multiple comparisons were made.
	  ○ Identification of predictors for RCD II – Continuous MR enteroclysis features were dichotomized by using cut-off levels determined by identifying the point where the sensitivity and specificity to detect RCD II were equal on the ROC
	  ○ Construction of scoring system – by utilizing independent predictors of RCD II
	• Validation group (n=40)
	  ○ Validation of scoring system in second group of patients
	  ○ Analysis of inter observer variation
	• Whole-group analysis (n=68)
	  ○ Survival analysis in all patients

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
	○ Calculation of accuracy for detection of malignancy
Length of follow up	28 months
Outcome	MR enteroclysis findings and validation of scoring system
Results	MR enteroclysis findings: Patient group comparisons in test group • No MR parameter differed significantly between patients with uncomplicated CD or RCD I • Median jenunal folds per 5cm lower in RCD II vs RCD I or CD • Splenic volume lower in RCD II vs RCD I • Diffuse bowel thickening and jenunoileal fold pattern reversal more frequently observed in RCD II than in CD • Mesenteric fat infiltration more prevalent in RCD II than RCD I Scoring system construction • Multivariate analysis showed following parameters to be independently associated with RCD II: ○ Presence of less than 10 folds per 5cm jejunum ○ Diffuse bowel wall thickening ○ Mesenteric fat infiltration • At optimal cut-off from ROC analyses of 2, none of 10 patients with RCD II were missed anf absence of RCD correctly diagnosed in 15/18 patients without RCD II • Readers disagreed for 9/40 studies on one feature • 6/9 discrepancies occurred in patients with RCD II • Agreement on: ○ 37/40 wall thickening ○ 37/40 mesenteric fat infiltration ○ 37/40 on <10 jejunal folds **see below for proposed scoring system

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**

Diagnostic accuracy of MR enteroclysis scoring system in test group
Sensitivity 100% (66 – 100), specificity 83% (58-96)

TP 10	FN 3
FP 0	TN 15

Diagnostic accuracy of MR enteroclysis scoring system in validation group
Sensitivity 87% (58 – 98), specificity 96% (78-100),

TP 13	FN 1
FP 2	TN 24

Survival analysis and detection of CD-related malignancy

- 14/68 patients died during follow-up
  - 2/41 with MR score of <2
  - 12/27 with MR score of ≥2
  - Diagnosis RCD II in 13/14 of those that died
  - Causes = EATL (n=8); sepsis (n=2); meningo-encephalitis (n=2); disseminated small-bowel carcinoma (n=1),

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
	malabsorption (n=1) • 5 year cumulative survival rate 95% in patients with MR score <2 compared with 56% in patients with an MR score ≥2
Source of funding	
Comments	
<u>Definintions</u>: **CD**: diagnosed based on the results of duodenal biopsies and positive serology for antihuman tTG and EMA in all patients Uncomplicated CD: diagnosed if during follow-up clinical symptoms and villous atrophy improved without the need for immunosuppressive therapy **RCD I:** diagnosed in case of persisting villous atrophy despite a GFD, but with normal phenotype of IEL's **RCD II**: diagnosed in case of persisting villous atrophy with abnormal phenotype IEL's **EATL** and adenocarcinoma: histological analysis of biopsy or resection specimens, and were established according to international consensus criteria Proposed scoring system: score calculated by adding total number of points • Number of jejunal folds per 5cm o ≥10 = 0 points o <10 = 1 point • Mesenteric fat infiltration o Present = 1 point o Absent = 0 point • Diffuse bowel wall thickening o Present = 1 point o Absent = 0 point Author conclusions: : MR enteroclysis can be used to investigate the presence of RCD II or malignancy in symptomatic patients with CD	

D.7 Review question 5.4

Bibliographic reference	**The American journal of gastroenterology 2000 95 (3) PAGES 712-714 Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery Dickey, W., Hughes, D. F.et al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if a consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? YES – 24 were excluded but explanation not given
Number of patients	53
Patient characteristics	Inclusion criteria: Presence of villous atrophy and positive IgA EMA Exclusion criteria: IgA deficiency, Non-compliance with diet or biopsy Age at diagnosis – mean (range): 51 years (16 – 81 years) Gender (M/F): 14/39 Immunoglobulin A (IgA) deficiency: None Time on gluten-free diet – mean (range) : 12 months Assessed by: Dietitian for adherence

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
Intervention	IgA EMA by indirect immunofluorescence using primate oesophagus (Biodiagnostics, Upto-upon-Severn, England) with a titer of ≥ 1.5 as cut-off Duodenal biopsy Dietitian assessment
Comparison	NA
Length of follow up	12 months
Location	Northern Ireland
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms 48/53 (90.6%) IgA EMA – number testing negative At 3 months = 13/53 (58% At 6 months = 50/53 (75%) At 9 months = not reported At 12 months = 46/53 (87%) Duodenal biopsy TVA/STVA at baseline (n = 41) At 12 months = 13 were normal, 18 had PVA and 10 were non-responders (persistent TVA/STVA) PVA at baseline (n = 12): At 12 months = 7 were normal, 1 was Marsh grade 1 and 4 were non-responders (persistent PVA) Growth in children and young people Not reported

Bibliographic reference	**The American journal of gastroenterology** **2000 95 (3) PAGES 712-714** **Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery** **Dickey, W., Hughes, D. F.et al.**
	Complications of coeliac disease Not reported Dietary adherence 5/53 (9.4%) reported as non-adherent Impact on carers Not reported Health-related quality of life Not reported
Source of funding	None reported
Comments	All responders were adherent to GFD, non-responders were non-adherent Of 79 candidates for inclusion, 2 were EMA negative at baseline due to IgA deficiency, and 62 test EMA positive at baseline, 9 did not have a full 12 months of GFD, only 53 EMA + at baseline were followed up Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Autoimmunity** **2007 40 (2) PAGES 117-121** **Two-year follow-up of anti-transglutaminase autoantibodies among celiac children on gluten-free diet: comparison of IgG and IgA** **Martin-Pagola, Ainhoa, Ortiz-Paranza, Lourdeset al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? YES – unclear if a consecutive sample was used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	93
Patient characteristics	Inclusion criteria: ESPGHAN diagnosis of CD with HLA-DRB! Typing and GFD adherent Exclusion criteria: Non-adherence to GFD Age at diagnosis – mean (range): 3.56 years (0.94 – 17.5) Gender (M/F): 35/58 (62.4% female) Immunoglobulin A (IgA) deficiency: Not reported

Bibliographic reference	**Autoimmunity** **2007 40 (2) PAGES 117-121** **Two-year follow-up of anti-transglutaminase autoantibodies among celiac children on gluten-free diet: comparison of IgG and IgA** **Martin-Pagola, Ainhoa, Ortiz-Paranza, Lourdeset al.**
	Time on gluten-free diet – mean (range): 2 years Assessed by: Not reported
Intervention	IgA anti-tTG IgG anti-tTG Both determined by immunoprecipitation radioassays. S25 labeled human recombinant tTGase was incubated with 3µl of serum at 4oC overnight and immune complexes were precipitated with a 25% (v/V) suspension of protein-A agarose (Amersham Biosciences, Barcelona, Spain) for IgG or a 20% (v/v) suspension of agarose-conjugated IgA specific antibodies (Sigma cat. No. A2691) St Louis, MO) for IgA. Cut-off values were set as the sum of the mean and 3/SD of the index values of 50 serum samples from the general population.
Comparison	NA
Length of follow up	24 months
Location	Spain
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms (reported as remission) Not reported Response – defined as number of people testing negative on serology At 6 months IgA: 46/93 (49%) IgG: 59/93 (63%) At 24 months IgA: 82/93 (88%) IgG: 90/93 (96%)

Bibliographic reference	**Autoimmunity** **2007 40 (2) PAGES 117-121** **Two-year follow-up of anti-transglutaminase autoantibodies among celiac children on gluten-free diet: comparison of IgG and IgA** **Martin-Pagola, Ainhoa, Ortiz-Paranza, Lourdeset al.**
	Biopsy – response = normal biopsy N = 41* Of those with Marsh 3a or 3b at diagnosis 4 (9%) were Marsh 2 12 (30%) were Marsh 1 25 (61%) were Marsh 0 Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Not reported Health-related quality of life Not reported
Source of funding	Funded by the Spanish Ministry of Health
Comments	Only 41 consented to a second biopsy after 2 year GFD Only those with elevated serology titers at baseline followed up

Bibliographic reference	**Autoimmunity** **2007 40 (2) PAGES 117-121** **Two-year follow-up of anti-transglutaminase autoantibodies among celiac children on gluten-free diet: comparison of IgG and IgA** **Martin-Pagola, Ainhoa, Ortiz-Paranza, Lourdeset al.**
	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**
Study type	Cohort
Study quality	Could the selection of patients have introduced bias? NO Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. Yes – unclear of exact timing of tests Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	20
Patient characteristics	Inclusion criteria: Diagnosed with CD with March 3 criteria Exclusion criteria: IgA deficiency

Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**
	Age at diagnosis – median (range): 62 years (29 – 86 years) Gender (M/F): 10/12 (54.5% female) Immunoglobulin A (IgA) deficiency: NA Time on gluten-free diet – mean (range) : 12 months Assessed by: Dietitian for adherence
Intervention	AGA (AGA was tested using UniCAP Gliadin IgA (Pharmacia Diagnostics, Uppsala, Sweden) and was defined as positive with a result >3 $mg_A\ L^{-1}$.) tTGgrh (Celikey®, tTGrh, IgA antibody assay (Pharmacia Diagnostics, Freiburg, Germany). It was defined by the producer as positive when >8 U mL^{-1}, negative when <5 U mL^{-1}, borderline between 5 and 8 U mL^{-1}) tTGgp (ImmuLisa®, tTGgp with guinea-pig-derived tTG (IMMCO, Buffalo, NY, USA). The result was defined by the producer as positive when >25 U, negative when <20 U, borderline when 20–25 U) IgA EMA (indirect immunofluoflourescence using monkey oesophageal tissue. Tissue sections from marmoset monkey oesophagus were mounted on microscopic slides. Undiluted sera and sera diluted 1 : 25 with phosphate-buffered saline (PBS) was applied to slides, which were incubated for 30 min at room temperature. After washing with PBS the sections were covered with fluorescein conjugated rabbit-antihuman IgA (Dako, Copenhagen, Denmark) for 30 min, washed with PBS and examined by fluorescence microscopy. Positive sera were further diluted (1 : 5, 1 : 10, 1 : 25, 1 : 100, 1 : 400 and 1 : 1600). Sera positive in dilution 1 : 10 or more were defined as positive Biopsy (Three to four biopsy specimens were obtained during upper endoscopic examination of each patient from the lower part of the duodenum descendens with standard forceps. All biopsies were fixed in a 4% buffered formaldehyde solution. Fixation, embedding and cutting were carried out according to routine methods)
Comparison	NA

Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**
Length of follow up	12 months
Location	Sweden
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms (reported as remission) 16/18 (88.9%) Response – defined as number of people testing negative on serology <u>AGA IgA</u> at 3 months =9/114 (74%) at 6 months = 14/15 (93%) at 9 months = not reported at 12 months = 15/15 (100%) <u>IgA EMA</u> at 3 months =7/17 (41%) at 6 months = 13/17 (65%) at 9 months = not reported at 12 months = 14/16 (87%) <u>IgA tTGrh</u> at 3 months = 8/14 (57%) at 6 months = 10/14 (71%) at 9 months = not reported at 12 months = 14/14 (100%)

Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**
	Biopsy – response = normal biopsy At 12 months = 16/18 (88.9%) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Not reported Health-related quality of life Not reported
Source of funding	Authors are research staff at Pharmacia Diagnostic manufactirers fo some of the testing kits but they state no financial support was received.
Comments	1 person excluded for IgA deficiency and 1 not included in results as they stopped the GFD 2 participants did not have a repeat biopsy at 12 months, Both non-responders at 12 months were in remission at follow-up biopsy but no timeframe reported Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Journal of internal medicine** **2004 256 (6) PAGES 519-524** **Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance** **Midhagen, G., Aberg, A. K.et al.**

Bibliographic reference	**Journal of pediatric gastroenterology and nutrition** **2011 53 (1) PAGES 55-60** **Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease** **Monzani, Alice, Rapa, Annaet al**
Study type	Cohort (Prospective)
Study quality	Could the selection of patients have introduced bias? YES – unclear of study numbers and how the sample were selected Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO

Bibliographic reference	**Journal of pediatric gastroenterology and nutrition** **2011 53 (1) PAGES 55-60** **Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease** **Monzani, Alice, Rapa, Annaet al**
Number of patients	28
Patient characteristics	Inclusion criteria: Newly diagnosed CD Exclusion criteria: None reported Age at diagnosis – median (range): 8.1 years (1 – 16.8 years) Gender (M/F): 11/17 (60.7% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – mean (range) : 12 months Assessed by: Dietitian for adherence
Intervention	a-DGP IgA (performed with Quanta Lite Gliadin IgA II with suggested cutoff of 20 arbitrary unites) a-DGP IgA+G (performed with Quanta Lite Celiac DGP screen with suggested cutoff of 20 arbitrary unites) anti-tTG gA (performed withEliA Celikey IgA with cutoff of 10U/ml) AGA IgA (perfomed wih EliA Gliadin IgA with cut-off of 10U/ml)
Comparison	NA
Length of follow up	12 months
Location	Italy
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported

Bibliographic reference	**Journal of pediatric gastroenterology and nutrition** **2011 53 (1) PAGES 55-60** **Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease** **Monzani, Alice, Rapa, Annaet al**

Complications of coeliac disease
Not reported

Dietary adherence
Accuracy of serology in detecting 'partially adherent' from 'strictly adherent'

	Partially adherent	Strictly adherent
a DGP IgA + at 2-4 months	7	8
a DGP IgA – at 2-4 months	1	5
a DGP IgA + at 6-8 months	4	1
a DGP IgA – at 6-8 months	1	7
a DGP IgA + at 9-12 months	4	1
a DGP IgA – at 9-12 months	3	10

	Partially adherent	Strictly adherent
a DGP IgA/G + at 2-4 months	7	9
a DGP IgA/G – at 2-4 months	1	4
a DGP IgA/G + at 6-8 months	5	2
a DGP IgA/G – at 6-8 months	0	6
a DGP IgA/G + at 9-12 months	9	3
a DGP IgA/G – at 9-12 months	0	8

<table>
<tr><td>Bibliographic reference</td><td>Journal of pediatric gastroenterology and nutrition
2011 53 (1) PAGES 55-60
Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease
Monzani, Alice, Rapa, Annaet al</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Partially adherent</td><td>Strictly adherent</td></tr>
<tr><td>Anti tTG IgA + at 2-4 months</td><td>8</td><td>7</td></tr>
<tr><td>Anti tTG IgA – at 2-4 months</td><td>0</td><td>6</td></tr>
<tr><td>Anti tTG IgA + at 6-8 months</td><td>4</td><td>5</td></tr>
<tr><td>Anti tTG IgA – at 6-8 months</td><td>1</td><td>3</td></tr>
<tr><td>Anti tTG IgA + at 9-12 months</td><td>5</td><td>5</td></tr>
<tr><td>Anti tTG IgA – at 9-12 months</td><td>4</td><td>6</td></tr>
</table>
<table>
<tr><td></td><td>Partially adherent</td><td>Strictly adherent</td></tr>
<tr><td>AGA IgA + at 2-4 months</td><td>3</td><td>1</td></tr>
<tr><td>AGA IgA – at 2-4 months</td><td>5</td><td>12</td></tr>
<tr><td>AGA IgA + at 6-8 months</td><td>1</td><td>0</td></tr>
<tr><td>AGA IgA – at 6-8 months</td><td>4</td><td>8</td></tr>
<tr><td>AGA IgA + at 9-12 months</td><td>0</td><td>1</td></tr>
<tr><td>AGA IgA – at 9-12 months</td><td>9</td><td>10</td></tr>
</table>
Impact on carers
Not reported

Health-related quality of life
Not reported
</td></tr>
<tr><td>Source of funding</td><td>‘Study was partially funded by a grant of the Regione Piemonte government’</td></tr>
</table>

Bibliographic reference	**Journal of pediatric gastroenterology and nutrition** **2011 53 (1) PAGES 55-60** **Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease** **Monzani, Alice, Rapa, Annaet al**
Comments	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
Study type	Cohort (Prospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
	Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	30
Patient characteristics	Inclusion criteria: Diagnosis of CD according to EPSGHAN criteria Exclusion criteria: None reported Age at diagnosis – mean (range): 6 (1 – 24 years) Gender (M/F): 13/17 (56.7% female) Immunoglobulin A (IgA) deficiency: 3/30 (10%) Time on gluten-free diet – mean (range) : 12 months Assessed by: Not reported
Intervention	IgA EMA Ig ARA
Comparison	NA
Length of follow up	12 months
Location	Greece
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Response – defined as the number of people testing negative on serology <u>IgA EMA</u> At 3 months = 17/30 (57%) At 6 months = 25/30 (83%) At 9 months = 17/30 (90%)

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
	At 12 months = 30/30 (100%) <u>Ig ARA</u> At 3 months = 23/30 (77%) At 6 months = 26/30 (87%) At 9 months = 30/30 (100%) At 12 months = 30/30 (100%) Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Health-related quality of life Not reported
Source of funding	None reported
Comments	This study reports that ‘as the half-life of IgA is shorter than that of IgG, the IgA antibodies respond more rapidly to gluten changes in the diet and, therefore, are more appropriate for the follow-up of CD patients” IgA AGA and IgG AGA examined with home-made kits also studied so data were not used in this review

Bibliographic reference	**Digestive diseases and sciences** **1999 44 (10) PAGES 2133-2138** **Clinical application of immunological markers as monitoring tests in celiac disease** **Fotoulaki, M., Nousia-Arvanitakis, S.et al**
	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Scandinavian journal of gastroenterology** **2013 48 (6) PAGES 764-766** **Rapid anti-transglutaminase assay and patient interview for monitoring dietary compliance in celiac disease** **Zanchi, Chiara, Ventura, Alessandroet al.**
Study type	Cohort (Prospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if a consecutive ample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO

Bibliographic reference	**Scandinavian journal of gastroenterology** **2013 48 (6) PAGES 764-766** **Rapid anti-transglutaminase assay and patient interview for monitoring dietary compliance in celiac disease** **Zanchi, Chiara, Ventura, Alessandroet al.**
	Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? YES – 35 (10%) of the study population did not report on dietary adherence
Number of patients	350
Patient characteristics	Inclusion criteria: ESPGHAN diagnosed CD Exclusion criteria: None reported Age at diagnosis – median (range): 14 (6 – 45) Gender (M/F): 123/227 (65% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – mean (range) : 24 months Assessed by: Not reported
Intervention	IgA -anti-tTG using ELISA methods (Eu-tTG, Eurospital, Trieste, IT) using manufacturers cut-offs (IgA <9 U/ml) Rapid test (Eu-tTG Quick, Eurospital, Trieste, IT) using manufacturers cut-off
Comparison	NA
Length of follow up	24 months
Location	Italy
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Response Not reported

<table>
<tr><th>Bibliographic reference</th><th>Scandinavian journal of gastroenterology
2013 48 (6) PAGES 764-766
Rapid anti-transglutaminase assay and patient interview for monitoring dietary compliance in celiac disease
Zanchi, Chiara, Ventura, Alessandroet al.</th></tr>
<tr><td></td><td>
Complications of coeliac disease
Not reported

Dietary adherence
Reported as diagnostic accuracy of detecting ‘self-reported’ partially adherent to GFD at 24 months
<table>
<tr><th></th><th>Partially adherent</th><th>Strictly adherent</th></tr>
<tr><td>IgA anti-tTG ELISA +</td><td>19</td><td>8</td></tr>
<tr><td>IgA anti-tTG ELISA -</td><td>24</td><td>264</td></tr>
</table>
<table>
<tr><th></th><th>Partially adherent</th><th>Strictly adherent</th></tr>
<tr><td>Rapid test +</td><td>19</td><td>5</td></tr>
<tr><td>Rapid test -</td><td>24</td><td>267</td></tr>
</table>
Impact on carers
Not reported

Health-related quality of life
Not reported
</td></tr>
<tr><td>Source of funding</td><td>Authors report no conflict of interests</td></tr>
<tr><td>Comments</td><td>Unclear if all data reported for rapid test
Participants were questioned about the number of dietary transgressions in previous six months but no further details given</td></tr>
</table>

Bibliographic reference	**Scandinavian journal of gastroenterology** **2013 48 (6) PAGES 764-766** **Rapid anti-transglutaminase assay and patient interview for monitoring dietary compliance in celiac disease** **Zanchi, Chiara, Ventura, Alessandroet al.**
	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**
Study type	Cohort (prospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR – not reported if a consecutive ample used Is there concern that the included patients do not match the review question? UNCEAR – age group not reported Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**
	Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	50
Patient characteristics	Inclusion criteria: Diagnosis of CD based on the presence of flattened intestinal villi on duodenal biopsy. Exclusion criteria: None reported Age at diagnosis – mean (sd): mean not reported range 6 – 11 years Gender (M/F): 17/33 (67% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – 24 months
Intervention	.IgA tTG
Comparison	NA
Length of follow up	24 months
Location	Romania
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported number of people with negative test results IgA tTG at 3 months = 34/50 (68%) at 6 months = 34/50 (68%) at 9 months – not reported at 12 months = 41/50 (82%) at 24 months = 40/50 (80%)

Bibliographic reference	**Laboratory Medicine** **2011 42 (8) PAGES 497-501** **Importance of the educational environment in the evolution of celiac disease** **Samasca, G., Iancu, M.et al.**
	Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence Not reported Impact on carers Not reported Health-related quality of life Not reported
Source of funding	The authors report no conflicts of interest.
Comments	Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
Study type	Cohort (Retrospective)
Study quality	Could the selection of patients have introduced bias? UNCLEAR not reported if a consecutive sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	70
Patient characteristics	Inclusion criteria: Newly diagnosed with CD Exclusion criteria: None reported Age at diagnosis – mean (sd): 39 years (11.1) Gender (M/F): 20/50 (71.4% female) Immunoglobulin A (IgA) deficiency: 0/70 (0%) Time on gluten-free diet – 36 months Assessed by: Not reported

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
Intervention	Anti-endomysium (EmA) which were determined semiquantitative by the technique of indirect immunofluorescence (IIF) using a commercial kit INOVA (NOVA Lite Monkey Oesophagus IFA Kit/Slides, USA) on a 5-μm-thin cryostat section of distal monkey oesophagus as antigen substrate. Patient samples were tested in dilutions ranging from 1 : 5 to 1 : 2560. The antibody titre was defined as the highest sample dilution yielding fluorescence. Titre below1 : 5 was considered negative. Anti-tissue transglutaminase class IgA (tTG-A) which were assayed using a commercial anti-tTG type IgA ELISA test kit (QUANTA LiteTM, INOVA Diagnostics, USA). The cut-off value provided was 25U. ELISA was performed in duplicate according to the manufacturer's instruction.
Comparison	NA
Length of follow up	36 months
Location	Greece
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Response reported as number of people testing negative serology among those who were strictly compliant <u>IgA EMA</u> At 6 months = 20/51 (39.2%) At 12 months = 37/51 (72.5%) At 36 months = 48/51 (94.1%) <u>IgA tTG</u> At 6 months = 10/51 (19.6%) At 12 months = 25/51 (49.0%)

Bibliographic reference	**Autoimmune Diseases** **2014, Article ID 623514, 7 pages, 2014** **Celiac disease in adult patients: specific autoantibodies in the diagnosis, monitoring, and screening,** **Trigoni, E., Tsirogianni, A et al**
	At 36 months = 41/51 (80.4%) Complications of coeliac disease Not reported Dietary adherence 19 were considered partially adherent while 51 were considered strictly adherent Impact on carers Not reported Health-related quality of life Not reported
Source of funding	No funding reported but conflicts of interest listed
Comments	Unable to calculate data for accuracy of detecting non-adherence Study did not report on agreement or correlation between serology and biopsy

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
Study type	Cohort (prospective)
Study quality	Could the selection of patients have introduced bias? NO Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? NO
Number of patients	101
Patient characteristics	Inclusion criteria: CD confirmed buy biopsy (Marsh 2 or March 3) and positive clinical response to GFD Exclusion criteria: None reported Age at diagnosis – median (range): 37 years (21 – 72) Gender (M/F): 22/79 (78.1% female) Immunoglobulin A (IgA) deficiency: (%) Time on gluten-free diet – 12 months Assessed by: Not reported
Intervention	Serum EmAs were detected by immunofluorescence, using commercial slides of monkey esophagus (The Binding Site Ltd., distributed by Alfa Biotech). Sera were tested, as indicated by the manufacturer, at a 1:10 initial dilution, with the inclusion of positive and negative controls in every batch of tests. CD EmA-negative sera were further tested at a 1:5 dilution, and no false-negative results were obtained.

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
	Used four commercially available sandwich ELISAs that use human recombinant antigen (h-tTG): h-tTG 1 (DRG Diagnostics, distributed by Pantec S.r.l.); h-tTG 2 (EU-tTG® IgA; Eurospital S.p.A); h-tTG 3 (Immunodiagnostik, distributed by Li StarFISH); and h-tTG 4 (CELIKEYTM; Pharmacia & Upjohn, which uses human recombinant antigen extracted from eukaryotic cells. The same evaluation was also carried out with a sandwich ELISA that uses guinea pig tTG antigen (gp-tTG; GENESIS Diagnostics, distributed by Pantec S.r.l Duodenal biopsy
Comparison	NA
Length of follow up	12 months
Location	Italy
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Response reported as number of people normal duodenal biopsy at 12 months Normal (mucosal recovery) = 12/101 (12%) Improvement (Marsh grade I) = 51/101 (50%) no change (Marsh grade II or III) = 38/101 (38%) Complications of coeliac disease Not reported Dietary adherence NA

Bibliographic reference	**Clinical chemistry** **2002 48 (6 Pt 1) PAGES 960-963** **Comparative evaluation of serologic tests for celiac disease diagnosis and follow-up** **Martini, Silvia, Mengozzi, Giulioet al**
	Impact on carers Not reported Health-related quality of life Not reported
Source of funding	None reported
Comments	Mean percentage changes in anti-tTG values were 81% (range, 75–86%) for h-tTG 1, 51% (range, 43–60%) for h-tTG 2, 51% (range, 42–61%) for h-tTG 3, 77% (range, 69–85%) for h-tTG 4, and 75% (range, 67–82%) for gptTG. The concordances of the different assays in both positive (persistent histologic impairment and positive serologic markers) and negative (reconstituted mucosa and negative serologic markers) individuals vs histologic score were 29% for h-tTG 1, 65% for h-tTG 2, 14% for h-tTG 3, 16% for h-tTG 4, and 19% for gp-tTG, compared with 48% for EmA testing.

Bibliographic reference	**Journal of human nutrition and dietetics : the official journal of the British Dietetic Association** **2013 26 (4) PAGES 349-358** **Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease** **Shepherd, S. J. and Gibson, P. R**
Study type	Cohort (prospective)
Study quality	Could the selection of patients have introduced bias? NO Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? Could the patient flow have introduced bias? YES not all recruited were assessed 7/57 (12%) not assessed
Number of patients	50
Patient characteristics	Inclusion criteria: newly diagnosed CD using EPSGHAN criteria Exclusion criteria: None reported Age at diagnosis – median (range): 44 years (18 – 71) Gender (M/F): 17/33 (71% female) Immunoglobulin A (IgA) deficiency: 0/50 (0%) Time on gluten-free diet – 12 months Assessed by: Dietitian for adherence
Intervention	Biochemical and haematological indices were measured in peripheral blood samples taken from all patients at entry to the studies and, additionally, at 3, 6 and 12 months for the newly-diagnosed cohort. These included a complete blood count, electrolytes, renal function, liver function tests and iron studies, as well as serum folate, vitamin B12, zinc, vitamin D, magnesium, calcium and phosphate, using routine methodologies. Patients also had a repeat and histopathological

Bibliographic reference	**Journal of human nutrition and dietetics : the official journal of the British Dietetic Association** **2013 26 (4) PAGES 349-358** **Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease** **Shepherd, S. J. and Gibson, P. R**
	examination of duodenal biopsies or close to 12 months after the initial assessment. Patients were then educated in a nutritionally adequate 'no detectable gluten' diet, which was recommended to be followed for life. Education included description of the five-food-group healthy-eating model, including recommended servings and attention to fibre and variety in the diet. At the first interview, all patients were asked to keep a 7- day food record. Patients were provided with a recording diary card and instructions for its completion. They were asked to record the type and brand of food and how much was eaten or drunk using household measures on each day for the 7-day period before the review appointment. Measuring cups, spoons and reference diagrams were provided. Recorded information was checked at the consultation Adherence to the GFD diet was evaluated in detail at every interview by direct questions about any gluten consumed, either accidentally or intentionally in the time since their last review, by specific questioning and, if available, by the 7-day food diary entries.
Comparison	NA
Length of follow up	12 months
Location	Australia
Outcomes measures and effect size	Resolution of gastrointestinal and non-gastrointestinal symptoms Not reported Growth in children and young people Not reported Complications of coeliac disease Not reported Dietary adherence

Bibliographic reference	**Journal of human nutrition and dietetics : the official journal of the British Dietetic Association** **2013 26 (4) PAGES 349-358** **Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease** **Shepherd, S. J. and Gibson, P. R**
	50/50 (100%) 5/50 (10%) did not meet target nutrient density* Impact on carers Not reported Health-related quality of life Not reported
Source of funding	Supported by a Dora Lush Scholarship from the NHMRC of Australia and a Grant in Aid from the Australian and New Zealand Coeliac Research Fund.
Comments	7 participants excluded from analysis due to incomplete follow-up This applied to four nutrients (fibre, vitamin A, calcium, zinc; and fibre, folate, calcium, iron) in two patients, two nutrients (fibre, folate; and thiamin, folate) in two patients, and one nutrient (fibre) in one. Inadequate nutrient intake was associated with inadequate overall food intake (in relation to EER) for fibre, thiamin, calcium, magnesium and folate ($P < 0.05$ Fisher's exact test). Only for iron ($P = 0.23$) and vitamin A ($P = 1.0$) was inadequate intake independent of volume of food eaten.

Bibliographic reference	**Gastroenterology Today** **2005 Issue 1 PAGES 11-12** **Dietitian-led Coeliac Clinic:A successful change in working practice in modern healthcare** **Wylie, c., Geldart., S., et al**
Study type	Before and after study
Study quality	Could the selection of patients have introduced bias? YES – Convenience sample used Is there concern that the included patients do not match the review question? NO Could the conduct or interpretation of the index test have introduced bias?. NO Is there concern that the index test, its conduct, or interpretation differ from the review question? NO Could the reference standard, its conduct, or its interpretation have introduced bias? NO Is there concern that the target condition as defined by the reference standard does not match the review question? NO Could the patient flow have introduced bias? YES – unclear of numbers in 'before' phase of study Study reports on 99 patients, 78 of whom were not previously under hospital review
Number of patients	99
Patient characteristics	Inclusion criteria: Adults with histology present CD Exclusion criteria: Not reported Age at diagnosis – Range: 23 – 86 (Mean or median not reported) Gender (M/F): 30/69 (69.7% female) Immunoglobulin A (IgA) deficiency: Not reported Time on gluten-free diet – mean (range) : Not reported Assessed by: Dietitian for adherence
Intervention	Introduction of a dietitian into a Coeliac clinic

<table>
<tr><th>Bibliographic reference</th><th>Gastroenterology Today
2005 Issue 1 PAGES 11-12
Dietitian-led Coeliac Clinic:A successful change in working practice in modern healthcare
Wylie, c., Geldart., S., et al</th></tr>
<tr><td>Comparison</td><td>12 months before introduction of dietitian</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>United Kingdom</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Resolution of gastrointestinal and non-gastrointestinal symptoms
Not reported

Growth in children and young people
Not reported

Complications of coeliac disease – reported at 1 year
<u>DEXA scan</u>
Normal = 41 (42%)
Ostopenia = 37 (39%)
Osteoporosis = 18 (19%)

19 were referred for gastroenterology review due to abnormal findings on serology or symptoms. Further investigation lead to 1 case of caecal carcinoma, hypo-thyroidism, iron deficiency anaemia in pregnancy and adjustment of B12 therapy

Dietary adherence
<table>
<tr><th></th><th>12 months pre-dietitian</th><th>12 months With Dietitian</th></tr>
<tr><td>Perceived dietary adherence</td><td>71 (72%)</td><td>76 (77%)</td></tr>
<tr><td>Actual dietary adherence</td><td>54 (54%)</td><td>65 (66%)</td></tr>
<tr><td>Satisfaction</td><td>42 (42%)</td><td>80 (100%)</td></tr>
</table>
Impact on carers</td></tr>
</table>

Bibliographic reference	**Gastroenterology Today** **2005 Issue 1 PAGES 11-12** **Dietitian-led Coeliac Clinic:A successful change in working practice in modern healthcare** **Wylie, c., Geldart., S., et al**
	Not reported Health-related quality of life Not reported
Source of funding	None reported
Comments	

Bibliographic reference	**Galli (2014) Histological recovery and gluten-free diet adherence: a prospective 1 year follow-up study of adult patients with coeliac disease.**
Study type	Prospective cohort study
Study quality	Moderate
Number of patients	N = 65
Patient characteristics	65 consecutive patients newly diagnosed with CD were included 72.3% female Median age = 38 years, range 18 - 70
Intervention	One year prospective follow up using: • A questionnaire of dietary adherence • serological testing to measure seroconversion • histological recovery investigated through intestinal biopsy

Bibliographic reference	Galli (2014) Histological recovery and gluten-free diet adherence: a prospective 1 year follow-up study of adult patients with coeliac disease.
	serology for Iga EMA, adherence, and histology assessed at baseline and post one year after instructed to follow a GFD.
Comparison	Not applicable.
Length of follow up	1 year
Location	Italy
Outcomes measures and effect size	• Overall, 81.5% of all patients were assessed to have adequate dietary adherence (ADA) • 18.5% had inadequate dietary adherence (IADA) • ADA grop n = 53; IADA n = 12 • 66% ADA and 0% IADA patients achieved complete histological recovery (p=0.0001) • In ADA patients, antibody seroconversion and symptoms were not significantly different between patients who had achieved complete histological recovery and those with partial recovery • Multivariate analysis revealed Marsh 3 C (complete villous atrophy) was a risk factor for incomplete histological recovery in ADA patients - OR = 8.74, 95% CI: 1.87, 40.83
Source of funding	Supported by grants from University Sapienza
Comments	
Data for serological recovery from IgA tTG and/or IgA EMA are presented in patients with complete and partical histological recovery respectively, meaning that it is impossible to asses serological recovery as a unique entity from histology recovery. Due to the fact that IgA tTG and/or IgA EMA was conducted on each patient and presented as a unitary ‘serology’ entity, and that this information is presented only as a proportion of those who showed histological recovery or not, the data on serological recovery in patients with CD 1 year post diagnosis is unable to be pooled with other contributing studies in this chapter.	

D.8 Review question 6.1

Bibliographic reference	**Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet** **Reference ID:**
Study type and aim	Prospective cohort study to establish aetiology of continued symptoms on a gluten-free diet (GFD)
Study quality	8. Could the selection of patients have introduced bias? NO – all patients who met retrospective inclusion criteria of referral for NRCD were included 9. Is there concern that the included patients do not match the review question? NO - – all patients were suspected of NRCD at the time of referral 10. Could the conduct or interpretation of the index test have introduced bias? NO – all tests are clearly detailed 11. Is there concern that the index test, its conduct, or interpretation differ from the review question? - NO index tests are as outlined in protocol. 12. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – reference standards were as outlined by protocol and clearly detailed 13. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – extensive investigation was undergone for each patient to ensure correct diagnosis of RCD 14. Could the patient flow have introduced bias? No – all patients given standard uniform assessment and followed up as appropriate. Follow-up was a minimum of 2 years for all patients. Unless obvious cause of NRCD immediately apparent, all patients underwent biopsy **Overall risk of bias: LOW:** All patients met inclusion criteria, were suspected of NRCD and underwent extensive investigation to prove RCD diagnosis**.**
Number of patients	Total N = 112
location	England
Patient characteristics	**Inclusion criteria:** Patients prospectively recruited who were referred with a diagnosis of non-responsive coeliac disease (NRCD) between 2002 and 2003. All patients had continued symptoms on a gluten free diet **Exclusion criteria**: none listed **Mean age**: 48.5 **Mean age at diagnosis**: 31 years **Mean years since diagnosis**: 3 years (1 – 12 years)

Bibliographic reference	Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet Reference ID:
Signs and symptoms	Lethargy 43% Diarrhoea 65% Abdominal pain 37% Weight loss 23% Nausea and vomiting 10% Anaemia 10% 2 symptoms = 49% 3 symptoms 20%
Investigations	Appraisal of CD diagnosis, history of symptoms, clinical exam, routine blood tests and assessment of diet and GFD compliance. 'Patients were then investigated according to usual clinical practice and subsequent findings'. Those who developed further symptoms were reinvestigated. Unless an obvious cause was immediately apparent, a further bowel biopsy was undertaken. Jumbo endoscopy forceps were used to obtain four samples that were carefully placed, mucosal surface upwards.
Length of follow up	All patients followed for a minimum of 2 years
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 12/112 (11%) • Gluten ingestion: 45/100 (45%) • Microscopic colitis: 11/100 (11%) • Bacterial overgrowth: 9/100 (9%) • Lactose intolerance: 7/100 (7%) • Inflammatory colitis 7/100 (7%) • IBS: 10/100 (10%) • RCD 9/100 (9%) Other causes: (all 1 - 2 %)

Bibliographic reference	Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet Reference ID:
	• Anorexia • Pancreatic insufficiency • Diverticular disease • Medication-induced diahorrea • Combined variable immunodeficiency • Colorectal cancer • Anorectal dysfunction • Human immunodeficiency virus
Source of funding	Not stated
Comments	
Definition of NRCD: Failure of expected symptomatic response to GFD Total N CD = 100 (after removal of 12 non-CD) After 2 years 78% reported being symptom-free	

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
Study type and aim	Cohort (retrospective) study to determine etiologies of NRCD
Study quality	1. Could the selection of patients have introduced bias? No – all patients who met inclusion criteria (predefined) were included. 2. Is there concern that the included patients do not match the review question? NO – all patients met review criteria and all data was checked by 2 clinicians to ensure consistency of interpretation of clinical information. Definitions for criteria

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
	of NRCD and RCD are clearly descibed 3. Could the conduct or interpretation of the index test have introduced bias? NO – index tests are described clearly 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO- index tests and interpretation match review protocol outline 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – all patients had biopsy which revealed villous atrophy 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – all patients underwent extensive evaluation to ensure that target condition was as specified in protocol. 7. Could the patient flow have introduced bias? NO – all patients who met all inclusion criteria were included, all received reference biopsy and index tests to determine diagnosis as appropriate **Overall risk of bias: LOW –** all patients, index tests, the reference standard, and target condition were as specified in protocol.
Number of patients	Total N = 113 consecutive patients identified as NRCD from a pool of 603 biopsy-confirmed CD patient
location	US
Patient characteristics	• **Inclusion criteria**: a database of all patients diagnosed with biopsy-proven CD between 2000 and 2006 was examined for cases of NRCD and RCD defined by criteria listed below. For analyses, RCD cases were grouped with ulcerative jejunitis (UJ) and enteropathy associated T-cell lymphoma (EATL). • **Exclusion criteria**: Individuals without definitive evidence of CD in the form of duodenal biopsy exam, or a skin biopsy in case of dermatitis herpetiformis were not included • **Mean age**: NA • **Mean age at diagnosis**: 42 years • **Mean years since diagnosis**: NA • **Mean duration of symptoms**: NA
Signs and symptoms	• Diarrhoea: 54% • Lethargy: 5%

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
	• Abdominal pain: 55% • Weight loss : 20% • Nausea and vomiting : NA • Anaemia: NA
Investigations	Clinical notes, lab data, and diagnostic tests performed were investigated for each individual patient to identify evidence of NRCD. All entries were reviewed twice for accuracy Patients believed to be at high risk were evaluated for T-cell clonality and aberrant T-cell markers.
Length of follow up	Mean follow up = 20 months (2 – 126 months)
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 14/113 (12%) • Gluten ingestion: 36% • Microscopic colitis: 6% • Bacterial overgrowth (SIBO): 6% • Lactose intolerance: 8% • Inflammatory colitis:NA • IBS: 22% • RCD: 10% Other causes: • Eating disorder • Peptic ulcer disease • Gastroparesis • Crohn’s disease • Fod allergy

Bibliographic reference	Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease Reference ID:
	• CVID • Duodenal adenoma
Source of funding	Not Stated
Comments	
Diagnostic criteria for NRCD: referral for evaluation of lack of response to a gluten free diet. Failure of clinical symptoms or lab abnormalities typical of CD to improve within 6 months after GFD. Recurrence of symptoms and/or lab abnormalities typical of CD while on GFD. Refractory CD definition: persistence of villous atrophy despite strict GFD and no evidence of another pathology, including overt lymphoma	

Bibliographic reference	Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach Reference ID:
Study type and aim	Cohort (retrospective) study to identify causes of persistent symptoms in patients with NRCD and characterise patients with RCD
Study quality	1. Could the selection of patients have introduced bias? NO – patients included in study if were referred to single centre for persistent symptoms after CD diagnosis and GFD 2. Is there concern that the included patients do not match the review question? NO – all patients met inclusion criteria and definitions for CD, RCD, and NRCD are outlined clearly 3. Could the conduct or interpretation of the index test have introduced bias? NO – all tests detailed clearly 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – Biopsy samples from original sample were retrieved where possible and re-reviewed for signs of CD. When original biopsy samples could not be obtained, diagnosis from initial report, re-biospy, and serology were used for CD diagnosis. 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – target condition clearly outlined and matches review question 7. Could the patient flow have introduced bias? NO – all patients who met criteria were recruited

Bibliographic reference	**Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach** **Reference ID:**
	Overall risk of bias: LOW: All patients, index tests, the reference standard, and target condition were as specified in protocol.
Number of patients	Total N = 55
location	US
Patient characteristics	• **Inclusion criteria**: patients who had been evaluated for NRCD between 1997 and 2001. Included in the study when a definite diagnosis of CD was secured based on the clinical picture, on biopsy findings compatible with CD, and on criteria met for diagnosis of NRCD or RCD (listed below). • **Exclusion criteria**: Patients excluded if the CD diagnosis was reversed based on absence of CD on biopsy and presence of other disease responsible for their symptoms • **Mean age NRCD**: 51.3 (21-80) • **Mean age RCD:** 66.1 (56-82) • **Mean age at diagnosis**: • **Mean years since diagnosis**:
Signs and symptoms	• Diarrhoea: 84% • Lethargy:37% • Abdominal pain: 52% • Weight loss :47% • Nausea and vomiting : 17% and 10%, respectively • Anaemia: 37% •
Investigations	Patient records and small bowel biopsy results were reviewed. Patients underwent a systematic sequential evaluation including: • detailed dietary review, • serological testing for CD • repeat small intestinal and • colonic biopsy,

Bibliographic reference	Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach Reference ID:
	• small bowel aspirates for quantitative culture, • 72 hr stool fat measurement • small bowel radiographic studies • CT body imaging. All tests were not done in patients if an obvious case of symptoms was found which resulted in resolution of symptoms Dietary assessment involved 3 steps: 1. Physician review and direct questioning regarding patient's perspective of GFD 2. Direct and detailed evaluation by a dietician expert in celiac disease and the GFD 3. Serological tests, primarily endomysial antibodies (EMA) and gliadin antibodies (AGA)
Length of follow up	
Outcome	Cause of non-responsive CD
Results	Primary causes of NRCD: • Incorrect CD diagnosis: 6/55 (11%) (49 patients with CD) • Gluten ingestion: 25/49 (51%) • Microscopic colitis: 5/49 (10%) • Bacterial overgrowth: 7/49 (14%) • Lactose intolerance :NA • Inflammatory colitis :NA • IBS: 4/49 (8%) • RCD: 9/49: (18%) Other causes: • Pancreatic insufficiency 6/49 • Protein losing enteropathy

Bibliographic reference	**Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach** **Reference ID:**
	True RCD cases- further investigations: • T-cell receptor gene rearrangement: 6/9 tested for T-cell receptor gene rearrangement – 2/6 positive • Bone mineral density: 7/9 measured. 6/7 (85%) had osteoporosis. Prevalence of osteoporosis in RCD significantly higher than NRCD (10/28, 35%).
Source of funding	
Comments	
NRCD definition: persistence or recurrence of symptoms for up to 12 months, despite presumed GFD RCD: defined as persistence of symptoms and evidence for histological injury despite adhering to GFD for up to 12 months When original diagnosis of CD not made in authors institution (49 cases), original biopsy slides were retrieved if possible/ 32 original specimens retrieved and reviewed by same GI pathologist. Diagnosis in remaining cases based on original biopsy report, repeat biopsy, serological markers for CD, and response to GFD. Of those without CD, diagnosis was IBS (2/6), protein losing enteropathy (1/6|), malrotation of the gut (1/6), wheat allergy (1/6) Whipple disease (1/6).	

Bibliographic reference	**Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease** **Reference ID:**
Study type and aim	Cohort study (retrospective and prospective) to investigate utility of continual monitoring of IEL immunophenotype and clonality in the surveillance of RCD
Study quality	1. Could the selection of patients have introduced bias? YES – paper states that the selection of patients was biased towards those with RCD and EATL, implying that patient data was selected, rather than all consecutive patients who met criteria being included 2. Is there concern that the included patients do not match the review question? NO – all patients match review criteria 3. Could the conduct or interpretation of the index test have introduced bias? NO – index tests are clearly outlined and

Bibliographic reference	**Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease** **Reference ID:**
	match review protocol 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO – index tests match protocol 5. Could the reference standard, its conduct, or its interpretation have introduced bias? No all patients had biopsy-confirmed CD 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO, target condition matches review question 7. Could the patient flow have introduced bias? YES – For patients with RCD, 15 studied retrospectively, 14 prospectively, 12 both retro and prospectively studied. This patient flow may bias the outcome **Overall risk of bias: QUESTION!?**
Number of patients	Total N = 90
location	UK
Patient characteristics	• **Inclusion criteria**: 90 patients with CD with or without complications were reviewed and followed up from 2004 – 2008 in the authors institutions. Three inc 33 pts with uncomplicated CD, 7 suspected RCD, 41 pts with EATL in whom a history of CVD was documented. Criteria used for diagnosis listed below • **Exclusion criteria**: none listed • **Mean age**: NA • **Mean age at diagnosis**: 50 • **Mean years since diagnosis**: NA
Signs and symptoms	N/A
Investigations	• Biopsy: A total of 220 duodenal biopsis taken at diagnosis and follow-up were studied: 47% retrieved retrospectively; 53% collected prospectively • Immunohistochemistry: double IHC for CDʒε and CD8 was performed. Percentage of CDʒε(+)CD8(-) obtained by counting cells in at least 100 labelled IEL's. • Clonality analysis: performed using BIOMED-2 multiplex PCR primer mixes and heteroduplex analysis of PCR

Bibliographic reference	Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease Reference ID:
	products with modifications. Each sample analysed in duplicate for both TCRG and TCRB gene rearrangements
Length of follow up	40 months (3-360)
Outcome	Utility in monitoring IEL and clonality in RCD patients
Results	• Biopsy immunophenotype and monoclonality in diagnostic biopsy: o Initial biopsy of well-characterised uncomplicated CD RCD and EATL used to establish cut-off value for diagnosing aberrant IEL immunophenotype. ≥040% optimal ROC cut-off to separate both RCD and EATL from CD o Aberrant immunophenotype found in 1/30 CD patients. This one patient went on to develop RCD and EATL o 73% RCD biopsy positive o 89% EATL specimens o Monoclonality present in 6/37 CD; 24/37 RCD; 17/17 RCD. o Aberrant immunophenoptye and monoclonality concurrent in majority of patients, more frequent in patients with RCD that later developed EATL (89%) • Aberrant immunophenotype and monoclonality in follow-up: o CD: 4/24 showed aberrant phenotype. 3 of these were non-compliant. Monoclonality detected in 3 patients who were also non-compliant. . 0/24 showed concurrent aberrant phenotype and monoclonality that persisted in 2+ consecutive biopsies. o Suspected RCD: 6/7 showed aberrant phenotype at last follow-up. Monocloclonality seen in 2/7 o RCD: 22/29 showed aberrant immunophenotype o EATL: ; 20/29 showed persistent monclonality ; 15/29 showed persistent concurrent monoclonality and immunophenotype • Rate of increase in CDʒε(+)CD8(-) IEL's during FCD follow-up: o 11 pts with RCD showed progressive increase in CDʒε(+)CD8(-) o 3 suspected RCD showed progressive increase in CDʒε(+)CD8(-)

Bibliographic reference	**Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease** **Reference ID:**
	○ Mean % of IEL;s in these cases was 18% at initial and 58% at last follow-up ○ Median rate f increase 1.8% per month 11/29 RCD patients developed EATL. Persistent aberrant immunophenotype was not associated with progression to EATL Persistent monoclonality was not associated with progression to EATL Combination of concurrent persistent immunophenotype and clonality was a predictive risk factor for EATL (p=0.02) Presence of persistent > 80% CDʒε(+)CD8(-) IEL's and monoclonality was strongest and only independent predictive factor of EATL development , p=0.001, OR 45 95% CI (4-506)
Source of funding	
Comments	
Criteria used to define: **CD**: clinical symptoms, positive for CD antibodies, histological evidence of CD, and clinical improvement on GFD **RCD:** persistent symptoms and villous atrophy, or deterioration on biopsies despite strict GFD for ≥ 12 months. Compliance rigorously checked by dietician and serology, and other causes of atrophy excluded **Suspected RCD:** not all criteria for RCD were fullfilled. Although adhering strictly to a GFD and having negative serology and no obvious clinical symptoms, patients continued to show villous atrophy for > 2 years. **EATL:** WHO classification of tumours of hematopoietic and lymphoid tissues Patients with CD: 14 studied retrospectively, 6 prospectively, 13 both retro and prospectively. 11 were poorly compliant to a GFD. Patients with suspected RCD: 2 prospectively and 5 retro and prospectively studied Patients with RCD: 15 retrospectively., 14 prospectively, 12 both retro and prospectively studied Author conclusions:	

Bibliographic reference	**Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease** **Reference ID:**
	1. Presence of aberrant immunophenotype and monoclonality of IEL's not specific to RCD as also seen in CD, although this is transient and ass with non-compliance to GFD 2. Aberrant immunophenotype and monoclonality in RCD nearly always persistent and often concurrent 3. Presence of persistent concurrent aberrant IEL immunophenotype, especially >80% CDϑε(+)CD8(-) IEL's, and monoclonaity in RCD biopsies is associated with development of EATL. 4. IEL alteration is progressive and accumulative and a high proportion of cases of RCD showing normal IEL phenotype and polyclonality at time of diagnosis gained aberrant immunophenotype and monclonality during follow-up.

Bibliographic reference	**Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease**
Study type and aim	Longitudinal prospective cohort study to examine potential of FDG PET in detection of EATL in RCD patients and compare to CT imaging
Study quality	**1. Could the selection of patients have introduced bias?** NO – consecutive patients were recruited 2. **Is there concern that the included patients do not match the review question?** NO- all patients were evaluated for RCD. RCD definition was clearly outlined and matched review criteria **3. Could the conduct or interpretation of the index test have introduced bias?** NO – 2 independent nuclear medicine physicians naïve to clinical detail reviewed scans 4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?** NO – index test is as specified in protocol 5. **Could the reference standard, its conduct, or its interpretation have introduced bias?** NO – Biopsy samples were all taken from the small biopsy and evaluated according to Marsh criteria **6. Is there concern that the target condition as defined by the reference standard does not match the review question?** NO – RCD diagnosis clearly defined and matches protocol **7. Could the patient flow have introduced bias?** NO, all patients included in analysis after appropriate excludiodn. All patients received same reference standard, and tests

Bibliographic reference	Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease
	Overall risk of bias: LOW – patient population, reference, and index tests all match review protocols.
Number of patients	Total N=38 patients; 30 patients with RCD, 8 patients with EATL
location	Netherlands
Patient characteristics	**Inclusion criteria:** consecutively-referred patients for evaluation of RCD and EATL. Definitions listed below **Exclusion criteria**: patients were excluded because of normal findings on duodenal histology, F-FDG PET, and abdominal CT **Mean age**: 63 (44-89) **Mean age at diagnosis**: NA **Mean years since diagnosis**: 5 (1-17)
Signs and symptoms	NA
Investigations	• Abdominal CT – pts fasted over night. Diluted solution of barium sulphate administered to patients. 1000mL of E.Z-CAT administered in 2 doses of 500mL night before and morning of scan. Additional E.Z.-CAT 200mL admin 15 mins before CT scan started and 100mL of intravenous iopromide (300mg/mL). Scan assessed for : o bowel thickening (abnormal, >3mm thick) o lymphadenopathy (abnormal >10 mm in size along short axis) o mesenteric fat infiltration • Whole-body F-FDG PET – all patients asked to fast for 6 hours before F-FDG injections and received IV N-butyl bromide 20mg 5 mins before scan. This repeated when necessary 45 mins after first injection. Emission and transmission scans of 5 and 4 mins per med position (ETTE mode) performed 60mins after injections of 370 MBq of F-FDG from neck to pelvic floor. Venous blood withdrawn before injection for measurement of serum glucose concentration. o Classified as negative when F-FDG uptake compatible with physiologic bio distribution o Equivocal o Positive when F-FDG uptake not compatible with physiological bio distribution • IgA AGA, IgA TTG, IgA EMA • HLA DQ2/DQ8

<table>
<tr><th>Bibliographic reference</th><th>Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease</th></tr>
<tr><td></td><td>• Small bowel histologic evaluation according to Marsh criteria
• Suspected sites of lymphoma sampled during small bowel enteroscopy and</td></tr>
<tr><td>Length of follow up</td><td>14 months (9-24months)</td></tr>
<tr><td>Outcome</td><td>F-FDG PET results compared to CT, histology findings on biopsy or resection, and surgical findings.</td></tr>
<tr><td>Results</td><td><u>FDG PET vs. Abdominal CT scan</u>

• EATL:
○ F-FDG PET identified enhanced abdominal F-FDG uptake in 8/8 (100%) EATL patients (95% CI: 67%-100%)
○ CT abnormal in 7/8 (87%) of EATL patients (95% CI: 52%-97%)

• RCD:
○ F-FDG PET identified enhanced abdominal F-FDG uptake in 3/30 (10%) RCD patients (95% CI: 3%-25%)
○ CT abnormal in 14/30 (47%) of RCD patients (95% CI: 30%-63%)

Abdominal CT
Sensitivity 88% (65 – 100), specificity 53% (35-71), PPV 33%, NPV 94%
<table><tr><td>TP

7</td><td>FP

14</td></tr><tr><td>FN

1</td><td>TN

16</td></tr></table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease</th></tr>
<tr><td></td><td>Positive F-FDG PET
Sensitivity 100% (100), specificity 90% (79 - 100), PPV 73%, NPV 100%
<table><tr><td>TP

8</td><td>FP

3</td></tr><tr><td>FN
0</td><td>TN
27</td></tr></table>
Abdominal CT results concordant with results of F-FDG PET in 7 patients (88%) who had EATL and in 18 patients (60%) with RCD. CT did not match PET in 1 patient (12/5%) with EATL and in 12 patients (40%) with RCD.</td></tr>
<tr><td>Source of funding</td><td></td></tr>
<tr><td colspan="2">Comments</td></tr>
<tr><td colspan="2">Definition for:
EATL: based on histologic and immunohistochemical features according to WHO classification of Tumors and haematopoietic and lymphoid tissues
RCD: symptoms of malabsorbtion due to persisting villous atrophy with crypt hyperplasia and increasel IEL despite adherence to a GFD and in the absence of over EATL

At follow-up 75% patients with EATL and 13% RCD patients had died

Abnormal CT findings in patients with evidence of EATL included lymphadenopathy (n=4), thickened small bowel wall (n=7), mesenteric fat infiltration (n=2)
Abdominal findings of enhanced F-FDG PET proven to be EATL by histological examination of samples obtained via surgical resection of the small bowel.

All RCD patients underwent small bowel enteroscopy – No histoligcal evidence of EATL was found.</td></tr>
</table>

Bibliographic reference	Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease
F-FDG PET showed equivocal findings in 3 patients (10%) with RCD. In thes pts, CT normal in 1 pt and abnormal in 2 (no evidence of EATL found on enteroscopy). When equivocal PET findings counted as positive in the analysis (n=6) the specificity declined to 80% but remained higher than CT (p=0.008). Author conclusion: F-FDG PET more sensitive in detecting EATL in patients with RCD than CT. Recommended to be used in addition to CT in evaluating patients with RCD.	

Bibliographic reference	Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae Refernce ID:
Study type and aim	Prospective cohort study to assess value of double-balloon enteroscopy in patients with RCD
Study quality	8. Could the selection of patients have introduced bias? YES – Unclear if consecutive recruitment 9. Is there concern that the included patients do not match the review question? NO – all patients met inclusion criteria for RCD and definition for RCD is described. 10. Could the conduct or interpretation of the index test have introduced bias? NO - 11. Is there concern that the index test, its conduct, or interpretation differ from the review question? YES – 24 samples taken from 21 patients, 3 of the same patients contribute to the analysis twice. It is not clear how this is accounted for in the analysis, which may bias results and their interpretation. 12. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – all biopsy reference standards taken within same time period from index test and graded according to Marsh criteria. 13. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – all patients met criteria for RCD and EATL 14. Could the patient flow have introduced bias? NO – all patients received biopsy and DBE. Data for CT and VCE was incomplete and therefore not included/ **Overall risk of bias: QUESTION**

Bibliographic reference	Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae Refernce ID:
Number of patients	Total N = 21
location	Netherlands
Patient characteristics	**Inclusion criteria:** consecutive patients referred to specialist centre for DBE between 2004 and 2005 all patients were symptomatic on a strict GFD for a median period of 60 months and were suffering from persistent villous atrophy on duodenal histology. **Exclusion criteria**: None listed **Mean age**: 61 (41-89) **Mean age at diagnosis**: NA **Mean years since diagnosis**:5 (0.3 – 33)
Signs and symptoms	17/21 were symptomatic: Lethargy NA Diarrhoea 11/21 (52%) Abdominal pain 3/21 (14%) Weight loss 3/21 (14%) Nausea and vomiting NA Anemia NA

Investigations	Primary:
	• Double balloon enteroscopy (DBE)
	  ○ Done within 4-6 weeks of initial duodenoscopy
	  ○ Endoscope and flexible overtube both provided with soft latex balloons connected through built-in air route to a controlled pump system.
	  ○ Advancement or withdrawal of scope achieved by deflating or inflating balloons
	  ○ Endoscope introduced orally in all patients
	  ○ Length of visualized small bowel was estimated by calculating su of each sequential progressive extension of the scope through overtue

Bibliographic reference	**Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae** **Refernce ID:**
	○ Patients prepared with Klean Prep bowel cleanse ○ Midazolam mean dose 10mg and mean dose 7.5 µg of fentanyl for conscious sedation ○ Small bowel assessed for a-priori defined low risk: reduction (≤ 3 per endoscopic field of view) or loss of folds, scalloping, nodularity or muscosa or mosaicism, visible vessels, after air insufflation. ○ Ulcerations at ;eat 5mm in diameter and stenosis were considered high risk lesions for their potential risk of harbouring malignancy ○ Endoscopic findings considered jejunal if were found in proximal 2-3 m of the calculated endoscopic insertion depth ○ Small bowel as visualized by DBE divided into proximal, distal, and middle, and 4 biopsies taken from each segment. Diagnostic workup prior to DBE: • IgA tTTG, IgA EMA CD antibodies • HLA DQ2/DQ8 genotyping • Eosophagogastroduodenoscopy • Abdominal CT (n=14) • Video capsule endoscopy (n=7)
Length of follow up	Median interval of 36 months
Outcome	Utility of DBE in examination of patients with RCD
Results	DBE findings: • Jejunal ulcerations which revealed presence of EATL found in 5/21 (24%) of patients (95% CI: 10-45%) • Ulcerative lesions in absence of histological evidence of EATL found in another 2 patients (9%; 95% CI: 2-28%). – histology of nonulcerative mucosa classified as Marsh 3 and therefore were considered to have ulcerative jejunitis • In remaining 14 patients (66%), low risk features i.e. flattened villi, loss of folds, scalloping, and nodularity were found by double balloon enteroscopy – these patients diagnosied wih RCD on basis of persistent villous atrophy despite GFD Esophagogastroduodenoscopy findings: • Could detect low-risk lesions in duodenum

Bibliographic reference	**Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae** **Refernce ID:**
	• Did not detect EATL nor ulcerative jejunitis in any patient CT findings: • Abnormal in 4 patients with EATL • Missed diagnosis of EATL in 1 patient • Missed both ulcerative jejunitis patients • Presence of EATL further suggested in 4/7 patients who had CT – after median 36month follow-up none of these patients developed lymphoma Author conclusions: complications of RCD like EATL and UJ can be efficiently detected or excluded by DBE
Source of funding	
Comments	
Duodenal and small bowel biopsies evaluated according to Marsh criteria Diagnosis of EATL: • Established according to WHO classification based o histological and immunohistochemical features and TCR gene rearrangement studies. • Immunohistochemical features are evidence of large or medium sized T-cell proliferation expressing CD3(+) CD8 (+-)and CD103(+) Standard esophagogastroduodenoscopy failed to diagnose 2 EATL patients due to limitations in introducing the endoscopy beyond ligament of Treitz Ulcers are more commonly located in the jejunum and ileum rather than duodenum and DBE more easily able to investigate these distal locations.	

Bibliographic reference	**Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma** **Reference ID:**
Study type and aim	Cohort study to analyse CT findings in RCD and EATL
Study quality	1. **Could the selection of patients have introduced bias?** UNCLEAR – unclear if all patiens were enrolled

Bibliographic reference	**Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma** **Reference ID:**
	consecutively into study **2. Is there concern that the included patients do not match the review question?** NO – all patients were enrolled according to diagnostic criteria as outlined in protocol. 3. **Could the conduct or interpretation of the index test have introduced bias? NO** – all scans were analysed by 2 radiologists in consensus for diagnostic parameters. 4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?** NO – test matches protocol 5. **Could the reference standard, its conduct, or its interpretation have introduced bias?** NO – all patients had CD and RCD confirmed by biopsy. **6. Is there concern that the target condition as defined by the reference standard does not match the review question?** UNCLEAR – criteria for diagnosis were not clearly outlined. Paper states #patients were diagnosed by clinical evaluation' 7. **Could the patient flow have introduced bias?** NO – all patients received reference standard and investigative procedure **Overall risk of bias: QUESTION**
Number of patients	Total N=46
location	Netherlands
Patient characteristics	**Inclusion criteria:** Patients presenting with CD between 2004 and 2005. All patients were previously diagnosed as having CD (UEGW criteria), RCD (type I or II), or EATL according to clinical evaluation, serology, and intestinal biopsy. Patients divided into 2 groups: • Group 1 = uncomplicated CD (n=14) and RCD type 1 (n=10) • Group 2 = RCD type II (n=15) and EATL (n=7) **Exclusion criteria**: none listed **Mean age**: 58 **Mean age at diagnosis**: NA **Mean years since diagnosis**: NA

Bibliographic reference	**Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma** **Reference ID:**
Signs and symptoms	NA

Investigations	CT scan:
	• CT evaluated for:
	  ○ Abnormalities of intestinal fold pattern
	  ○ Bowel dilatation
	  ○ Air excess
	  ○ Fluid excess
	  ○ Bowel thickening
	  ○ Intestinal intussception
	  ○ Ascites
	  ○ Lymphadenopathy
	  ○ Increased no# of lymphnodes
	  ○ Mesenteric vascular changes
	  ○ Splenic size
	• Indications for CT were assessment of unexplained recurrent abdominal complaints and/or suspicion of EATL
	• 43/46 patients received orally admin diluted solution of barium sulphate suspension night before and morning of and 45 mins prior to imaging
	• 3 patients did not received oral contrast due to refusal
	• IV non-ionic contrast was admin in 42 patients (2 refused and 2 allergic)

Length of follow up	
Outcome	Findings of abdominal CT scan
Results	• Fold pattern and small bowel dilation ○ Fold could only be analysed in 26 patients ileal fold in 29 (lack of contrast or of distal tension of bowel loops)

Bibliographic reference	**Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma** **Reference ID:**
	○ 10/26 (38%)patients showed decrease in number jejunal folds ○ 16/26 (62%) increase in number of folds ○ Ileal folds increased in 5/29 (17%) and decreased in 24 (83%) ○ Small bowel dilation 11/46 • Fluid air excess ○ 24/46 – not visible ○ 14/46 – mild ○ 7/46- moderate ○ 6/49 – severe ○ All findings equally distributed between groups • Wall thickness and intussusception ○ Increase WT from 4 – 11mm in group 1 and from 5-15 in group 2 ○ 9/22 patients in group 2 showed thickened >1cm vs only 4 in group 1 ○ Intersussception observed in only 1 patient in group 1 compared to 5 patients in group 2 • Lymph nodes ○ Enlarged LN found in 5/22 patients in group 2 and 0 patients in group 1 • Vascular findings ○ Increase in number of small mesenterial vessels 20/24 (83%) patients in group 1 vs 12/22 (50%) n group 2 • Splenic volume ○ No signif diffs between groups ○ If divide patients into 3 arbitrary groups according to splenic volume, group 2 showed significantly more patients with smaller spleen than group 1
Source of funding	
Comments	
NOTE: Hadithi second author on paper. – most likely SAME COHORT of patients as in Hadithi 2007 study (recruited between 04 and 05).	

Bibliographic reference	**Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma** **Reference ID:**
Author conclusions: CT useful tool in discriminating between CD and (pre)EATL	

Bibliographic reference	**Daum (2007): Capsule endoscopy in refractory celiac disease** **Reference ID:**
Study type and aim	Retrospective cohort study to examine whether CE was able to detect ulcerative jejunitis or intestinal T-cell lymphomas that were missed by standard endoscopic and imaging procedure in patients with RCD
Study quality	1. **Could the selection of patients have introduced bias?** 2. **Is there concern that the included patients do not match the review question?** 3. **Could the conduct or interpretation of the index test have introduced bias?** 4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?** 5. **Could the reference standard, its conduct, or its interpretation have introduced bias?** 6. **Is there concern that the target condition as defined by the reference standard does not match the review question?** 7. **Could the patient flow have introduced bias?** **Overall risk of bias:**
Number of patients	Total N = 14 ; 7 Type I RCD and 7 type II RCD
location	Germany
Patient characteristics	**Inclusion criteria:** consecutive patients with RCD who presented between 2002 and 2005. RCD defined as below. **Exclusion criteria**: **Mean age**: 51 **Mean age at diagnosis**: **Mean years since diagnosis**: RCD type I = 78 months (12-130); RCD II 24 months (1-372)

Bibliographic reference	**Daum (2007): Capsule endoscopy in refractory celiac disease** **Reference ID:**
Signs and symptoms	NA

Investigations	• Wireless capsule endoscopy (CE)
	  ○ Patients receive 2 litres polyethylene glycol solution 4 hrs before investigation as well as 15mL simethicone
	  ○ Capsule images were assessed for signs of ulceration and tumours
	• Upper and lower endoscopy* see comment below
	• Abdominal CT or MRT

Length of follow up	RCD I = 27 months (2-24), RCD II = 12 (2 – 32)
Outcome	CE and CT findings in RCD patients
Results	Assessment of small bowel by CE completed in 9/14 patients. Incomplete in 1/7 RCD type 1 patients and 4/7 RCD II patients RCD type I: • Proximal villous trophy on WCE – 6/7 • Proximal villous atrophy confirmed by histology – 7/7 • distal villous trophy on WCE – 3/6 • distal villous atrophy confirmed by histology 3/6 • EATL seen on CE – 0 • EATL diagnosed by CT – 0 • Final diagnosis of overt EATL (including follow-up period) – 0 RCD type II: • Proximal villous trophy on WCE – 5/7 • Proximal villous atrophy confirmed by histology – 7/7 • distal villous trophy on WCE – 1/3 • distal villous atrophy confirmed by histology 3/6 • EATL seen on CE – 1 • EATL diagnosed by CT – 1

Bibliographic reference	Daum (2007): Capsule endoscopy in refractory celiac disease Reference ID:
	Final diagnosis of overt EATL (including follow-up period) – 3
Source of funding	None declared
Comments:	
RCD definition: increase of intraepithelial lymphocytes and persisting villous atrophy for more than 6 months or deterioration of malabsorption due to villous atrophy requiring therapeutic intervention in spite of strict GFD, after exclusion of defined causes. Type I: Type II: Classified as Type II when when T-cell antigen loss and/or T-cell clonality in the duodenum (as determined by T-cell PCR) CD diagnosed according to ESPGHAN criteria *CT/MRT with enteroclysis done in 8 patients; CT/MRT without enterocysis done in 4 patients; 2 patients refused radiological investigation Author conclusion: In patients with RCD type II, wireless CE can provide further info in detection of intestinal lymphoma. Also confirms low yield of routine imaging procedures including wireless CE in patients with RCD type I	

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
Study type and aim	Retrospective cohort study to describe VCE findings in NRCD and identify VCE findings associated with poor prognosis
Study quality	8. Could the selection of patients have introduced bias? 9. Is there concern that the included patients do not match the review question? 10. Could the conduct or interpretation of the index test have introduced bias? 11. Is there concern that the index test, its conduct, or interpretation differ from the review question? 12. Could the reference standard, its conduct, or its interpretation have introduced bias? 13. Is there concern that the target condition as defined by the reference standard does not match the review question?

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
	14. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N = 48
location	Netherlands
Patient characteristics	**Inclusion criteria:** all adults who underwent VCE for evaluation of persisting symptoms despite GFD at specialist centre between 2005 and 2010. Patients divided into four classifications: Uncomplicated CD (n=22), RCD I (n=12), RCD II (n=11), EATL (n=3) **Exclusion criteria**: For EATL patients; patients were excluded if they had a diagnosis of primary EATL, with no diagnosis of CD prior to developing EATL. **Mean age**: • uncomplicated:49 (18.5) • RCD I: 62 (9.8) • RCD II: 63 (9.8) • EATL: 64 (1.7) **Mean age at diagnosis**: • uncomplicated:42 (18.6) • RCD I: 49 (13.4) • RCD II: 55 (15.5) • EATL: 60 (3.7) **Mean years since diagnosis**: NA
Signs and symptoms	Lethargy - NA Diarrhea – 24/48 (50%) Abdominal pain – 8/48 (17%) Weight loss – 12/48 (25%)

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
	Nausea and vomiting - NA Anemia - 2/48 (4%)

Investigations	• VCE
	  ○ Performed only in absence of signs suggestive of small-intestinal stenosis
	  ○ 2L polyethylene glycol bowel preparation
	  ○ Small intestine divided into proximal (first ¼) and a distal part (remaining ¾) based on small-bowel transit time (SBTT)
	  ○ When small bowel exam incomplete, used transit data from complete studies and defined proximal small intestine as part of visualized within 2 SD of mean ¼ of the SBBT of complete studies
	  ○ Proximal and distal part of all VCE studies were reviewed for signs derived from previous publications on VCE or conventional endoscopy in CD, inc:
	  ▪ Villous atrophy
	  ▪ Mosaic pattern
	  ▪ Scalloping of folds
	  ▪ Mucosal fissures
	  ▪ Erosions
	  ▪ Ulcers
	  ▪ Strictures
	  ▪ Masses
	  ○ Size of erosion and ulcers classified arbitrary as either small (≤5mm), intermediate (5-10 mm), or large (>10mm).
	• Small bowel biopsy
	  ○ Obtained during esophagogastroduodenoscopy and/or DBE within 2 months of VCE
	  ○ Graded according to Marsh classification
	• T-cell flowcytometry
	
	• Double-balloon endoscopy

Bibliographic reference	**Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease** **Reference ID:**
Length of follow up	For Uncomplicated and RCD patients, mean follow up 25 months. For EATL patients, 2 months.
Outcome	VCE, flowcytometry, findings in uncomplicated, RCD and EATL patients
Results	Other causes of NRCD found in 17 patients: • Gluten ingestion: 14 • Lactose intolerance: 2 • Inflammatory colitis: 1 VCE findings: No clear relationship between size and number of erosions or ulcers and final diagnosis. 2 patients (RCD I and uncomplicated CD) diagnosed with ulcerative jejunitis Most abnormalities encountered in proximal small bowel Comparison according to prognosis: low risk (uncomplicated RCD and RCD I) vs high risk (RCD II and EATL) Presence of proximal focal erythema associated with risk of poor prognosis (i.e. diagnosis of RCD II or EATL) Absence of progression of the capsule to the distal intestine was associated with increased risk of poor prognosis (i.e. diagnosis of RCD II or EATL). No patients without these features died at follow up 2/15 (13%) patients with one of these died at follow-up 4/5 (80%) patients with both of these features died at follow-up **Author conclusion**: VCE minimally invasive endoscopic modality that could be of use in identifying patients with NRCD who require urgent and intensive medical treatment
Source of funding	
Comments	
Definitions:	

Bibliographic reference	Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease Reference ID:
Uncomplicated CD: diagnosed if during follow-up clinical symptoms, villous atrophy, and positive serology improved without need for immunosuppression, or if an alternative reason for symptoms was established **RCD**: defined by persistent or recurrent malabsorbtive symptoms and villous atrophy despite strict GFDfor at least 6 months in the absence of other causes. **RCD type I**: characterised by normal, polyclonal immunophenptype of IEL's with favourable response to nutritional support and immunosuppressive therapy **RCD type II:** characterised by presence of intraepithelial lymphocytes immunophenotype or by differences in clonality of the T-cell receptor (TCR) gene. Abnormal phenotype (>20% of the CD 103(=)/CD45(+) IEL's lacking surface CD3 on flowcytometry). **EATL**: diagnosis based on international WHO criteria. Divided into primary and secondary. Primary excluded. Secondary is when patients were known to have CD prior to EATL diagnosis **Ulcerative jejunitis:** defined as presence of ≥ 3 ulcers in the jejunum during enteroscopy	

Bibliographic reference	Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue Reference ID:
Study type and aim	Retrospective cohort study to define underlying and accompanying diseases and clinical outcome in consecutive patients with refractory sprue (RS)
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N =32 (23 RCD I, 9 RCD II)
location	Germany

Bibliographic reference	**Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue** **Reference ID:**
Patient characteristics	**Inclusion criteria:** patients with RCD who presented at specialist tertiary referral centre between 1993 and 2005 and underwent standardized investigation program. Criteria defined below. Inadvertant persisting gluten intake was excluded through repeated dietary counselling **Exclusion criteria**: patients with manifest lymphoma were excluded **Mean age**: 50.5 (17-75) **Mean age at diagnosis**: NA **Mean years since diagnosis**: NA
Signs and symptoms	NA
Investigations	
Length of follow up	55 months (12-372)
Outcome	Investigative findings of underlying and accompanying diseases in RCD .
Results	Primary findings: • IEL's significantly higher in patients with RCD I than RCD type II • 2 patients with RCD developed persisting concal –cell receptor rearrangements and loss of T-cell receptor β during follow-up and were accordingly reclassified as RCD II • 2 patients with RCD I showed signs of collagenous sprue • Other underlying diagnoses in RCD I: o Autoimmune enteropahy – n=2 o Immune reconstruction syndrome – n=1 o Common variable immune disease – n= 1 Accompanying diseases • 9 (28%) RCD patients developed thrombolytic complications (mean age 41 (17-55)). • Thrombolytic similarly frequent in RCD I and RCD II • 17 (53%) RCD patiebts uffered from autoimmune diseases other than CD: o Autoimmune hepatitis – n=4

Bibliographic reference	Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue Reference ID:
	○ Diabetel mellitis – n= 2 ○ Ulcerative colitis – n=2 ○ Autoimmune haemolytic anemia – n=1 ○ Collagenous colitis - n=2 ○ Hashimotos thyreoditis – n=1 ○ HLA-B27-positive polyarthritis – n=1 ○ Organizing pneumonia – n=1 ○ Primary bilary cirrhosis – n=1 ○ Scleradoma – n=1 ○ Systemic lupus – n= 1 ○ Threeoiditis De Quervain – n=1 ○ Type A gastritis – n=1 • Autoimmune disease accorrued in 13 patients with RCD I and 4 patients with RCD II and were not associated with CD : 11 with CD and 6 without CD • Osteopenia was detected in 12 patients; 6 RCD I and 6 RCD II Mortality and development of overt intestinal non-Hodgkin lymphoma • 8 patients died within follow-up period (4 from each RCD type) • 5 year cumulative survival was 90% (76-100) in patients with RCD I • 5 year cumulative survival was 53% (12-94) in patients with RCD II • The 4 RCD type I patients died from pneumonia • 4 patients with RCD II developed from lymphoma
Source of funding	
Comments	
Definitions: **RCD**: partial villous atrophy or worse (Marsh 3a-c)' introduction of a GFD resulting in neither clinical nor histological response within 6 months or persistent	

Bibliographic reference	Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue Reference ID:
villous atrophy ad clinical deterioration requiring therapeutic intervention. **RCD type II**: diagnosed with RCD II in the case of T-cell antigen loss (CD8 and/or T-cell receptor-β to less than 50% in IEL's on immunohistochemistry), T cell clonality, or both abnormalities in the duodenum as determined by T-cell receptor gene PCR	

Bibliographic reference	Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease Reference ID:
Study type and aim	Retrospective cohort study to investigate the contribution of IEL parameters toward mortality and morbidity in RCD
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N = 77 (RCD n=67, RCD II n=6)
location	U.S
Patient characteristics	**Inclusion criteria:** records from 700 biopsy-proven CD patients reviewed and all patients who met criteria for diagnosis of RCD were included (see below for definition). **Exclusion criteria**: any patients with other possible causes of villous atrophy, or those who presented with over EATL **Mean age**: 56 (16-87)

Bibliographic reference	**Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease** **Reference ID:**
	Mean age at diagnosis: NA **Mean years since diagnosis**: 60 months (1- 408)
Signs and symptoms	

Investigations	• Histopathology
	  ○ Taken at time of RCD diagnosis
	  ○ Degree of atrophy determined using Marsh-Oberhuber classification – dichotomised in analysis as mild (Marsh 3a) and severe (Marsh 3b-c)
	  ○ Biopsies also evaluated for presence of collagenous sprue and colonic biopsies for microscopic colitis
	• Immunohistochemistry
	  ○ Staining of small biopsies using indirect immunoperoxidase technique with antibodies directed against human T-cell antigens CD3 and CD8
	  ○ Percentage of CD3 (=) IEL's that expressed CD8 was calculated, and cases with <50% of IEL's expressing CD8 were considered abnormal (i.e. <50% CD3+ CD8+)
	  ○ ≥50% CD3+CD8+ considered normal
	• TCR gene rearrangement analysis
	  ○ PCR analysis for TCR gene rearrangement was performed using DNA extracted from biopsies used in immunohistochemical staining
	  ○ TCR-ỹ gene V-J region was amplified by multiplex PCR followed by heteroduplex analysis and polycarbamide gel electrophosphoresis.
	  ○ Presence of 1 positive peak was considered monoclonal, smear pattern polycloncal, and 2 (or more) distant peaks oglioclonal
	• Disease classification
	  ○ Refractoriness to GFD considered primary if there was no initial clinical response to GDF and secondary if symptoms recurred after initial response
	  ○ Patients with monoclonal TCR gene rearrangement were considered as having RCD II and those with polycloncal or oglioclonal results as having RCD type I

Bibliographic reference	**Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease** **Reference ID:**
Length of follow up	21 months (1 – 102)
Outcome	Outcomes of histopathology, immunohistochemistry, TCR PCR and disease classification investigations in RCD patients

Results	**RCD type I**
	• Histopathological outcomes:
	  ○ Mild atrophy – 42/67 (63%)
	  ○ Severe atrophy 25/67 (37%)
	• Immunohistochemical outcomes
	  ○ >50%: 43/67 (64%)
	  ○ <50%: 24/67 (36%)
	• TCR gene rearrangement outcomes
	  ○ Polyclonal: 59 (88%)
	  ○ Monoclonal: 0
	  ○ Oglioclonal8 (12%)
	• Lymphoma and morbidity
	  ○ Death: 0
	  ○ No lymphoma: 66 (99%)
	  ○ Non-EATL lymphoma 1 (2%)
	  ○ Autoimmune disease: 33 (49%)
	  ○ Associated CD diseases: 40 (60%)
	  ○ Other comorbid disease: 19 (28%)
	
	RCD type II
	• Histopathological outcomes:
	  ○ Mild atrophy – 1/6 (17%)
	  ○ Severe atrophy 5/6 (83%)
	• Immunohistochemical outcomes

Bibliographic reference	Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease Reference ID:
	○ >50%: 0% ○ <50%: 6/6 (100%) • TCR gene rearrangement outcomes ○ Polyclonal: 0 ○ Monoclonal: 6 (100%) ○ Oglioclonal: 0 • Lymphoma and morbidity ○ Death: 3 (50%) – All had monoclonal gene rearrangement ○ No lymphoma: 4 (76%) ○ Non-EATL lymphoma 2 (33%) ○ Autoimmune disease: 3 (50%) ○ Associated CD diseases 4 (67%) ○ Other comorbid disease: 4 (67%) • After 8.5 years follow-up all patients with moncloncal TCR showed clinical worsening, whereas polycloncal TCR group and oligocloncal groups showed only half (56% and 50% respectively) • Incidence of clinical worsening in patients with <50% or >50% CD3+ CD8+ IEL's was 7-% compared to 51%, respectively Kaplan-Meir progression-free survival curves showed shorter time until onset of severe symptoms when monoclonal TCR gene rearrangements or <50% CD3+ CD8+ IEL's were detected • Patients with monoclonal TCR rearrangement had a median overall progression-free period of 11 months (95% CI, 0.6 – 24months), compared with patient who had polycloncal rearrangement patterns, for whom period was 38 months (95% CI, 22- 54 months) • Same for immunohistochemistry, those who presented with <50% IEL's presented with severe symptoms earlier than those with >50% (21months vs 66 months) • RCD patients at higher risk than normal CD patients in developing comorbidities • Comorbid diseases found in 80% of all patients - no difference between RCD type I and type II • Most common autoimmune diseases:

Bibliographic reference	**Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease** **Reference ID:**
	○ Osteopenia or osteoporosis (n-33) - ○ Microscopic colitis (n=15) ○ Peripheral neuropathy (n=12) ○ Diabetes melitis type 1 (n=7) • Predictors of clinical worsening: ○ Monoclonal TCR ○ IEL pheonotype x serology ▪ Patients with <50% CD3+CD8+ IEL's and negative serology were at increased risk for premature clinical worsening <u>Author highlights:</u> • These findings highlight the value of detecting <50% CD3+CD8+ IEL's, alone, or in combination with serology, in predicting the worsening of clinical symptoms in RCD patients. • Patients with oligoclonal TCR gene rearrangement have a benign clinical course comparable to patients with polyclonal TCR gene rearrangement, hence, detection of this polyclonal gene rearrangement pattern by PCR shouldn't be used to classify patients as having RCD type II
Source of funding	
Comments	
<u>Diagnostic criteria:</u> **RCD**: patients with persistent villous atrophy (Marsh 3) in the follow-up biopsy and with persistent or recurrent symptoms despite being on a GFD for at least 12 months	

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
Study type and aim	Retrospective cohort study to determine MR enteroclysis findings in patients with uncomplicated CD, RCDI, and RCD II, and to determine diagnostic accuracy of MR enteroclysis to detect CD-related malignancies
Study quality	8. Could the selection of patients have introduced bias? 9. Is there concern that the included patients do not match the review question? 10. Could the conduct or interpretation of the index test have introduced bias? 11. Is there concern that the index test, its conduct, or interpretation differ from the review question? 12. Could the reference standard, its conduct, or its interpretation have introduced bias? 13. Is there concern that the target condition as defined by the reference standard does not match the review question? 14. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	Total N=68
location	Netherlands
Patient characteristics	**Inclusion criteria:** From VU hospital MR database, authors identified 80 MR enteroclysis studies that were obtained between 2004 and 2009 in 72 patients who experienced symptoms despite being on a GFD. Consecutive studies obtained from Sept 2004 – Dec 2005 were included in the test group and used to construct a scoring system to predict RCD II. Consecutive studies obtained from January 2006 – July 2009 were included in the validation group and used to validate the scoring system. • Test group – n=28 • Validation group - n=40 **Exclusion criteria**: follow-up studies (n=12) obtained after chemotherapy and/or autologous hematopoietic stem cell transplantation for RCD or enteropathy-associated T-cell lymphoma were excluded **Mean age**: 56 (18-81) **Mean age at diagnosis**: NA

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
	Mean years since diagnosis: NA:
Signs and symptoms	Lethargy - NA Diarrhea – 5/68 (7%) Abdominal pain – 21/68 (31%) Weight loss – 34/68 (50%) Nausea and vomiting – 3/68 (4%) Anemia - NA
Investigations	MR enteroclysis • Overnight fast, 9-F nasojejunal tube positioned distal to duodenojejunal junction with fluoroscopic guidance • During MR imaging, a minimum of 2000mL of 0.5% methylce3llulose solution in water was infused through the tube, at a flow rate of 80-100mL/min using MR compatible pump system. No IV contrast used • Imaging ceased when optimal distension of the full small bowel and cecum was obtained • No antispadmodics administered • Number of jejunal folds and ileal folds per 5cm calculated by using maximum value of three measurements for each loop • Small bowl thickening was considered to be present when the wall thickness of a distended small-bowel loop was more than 3mm • Itaussception defined as a target mass or a complex layered mass within the bowl luman • Lymph nodes larger than 1cm in diameter in their shortest axis considered enlarged • Mesenteric fat infiltration defined as decrease in signal intensity of mesentry surrounding mesenteric vessels **Study Pipeline:** • Test group (n=28) o Patients grouped into uncomplicated CD; RCD I or RCD II (see diagnostic criteria below) o Comparison of diagnostic groups – NB this is exploratory only, no corrections for multiple comparisons were

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**
	made. ○ Identification of predictors for RCD II – Continuous MR enteroclysis features were dichotomized by using cut-off levels determined by identifying the point where the sensitivity and specificity to detect RCD II were equal on the ROC ○ Construction of scoring system – by utilizing independent predictors of RCD II • Validation group (n=40) ○ Validation of scoring system in second group of patients ○ Analysis of inter observer variation • Whole-group analysis (n=68) ○ Survival analysis in all patients ○ Calculation of accuracy for detection of malignancy
Length of follow up	28 months
Outcome	MR enteroclysis findings and validation of scoring system
Results	MR enteroclysis findings: Patient group comparisons in test group • No MR parameter differed significantly between patients with uncomplicated CD or RCD I • Median jenunal folds per 5cm lower in RCD II vs RCD I or CD • Splenic volume lower in RCD II vs RCD I • Diffuse bowel thickening and jenunoileal fold pattern reversal more frequently observed in RCD II than in CD • Mesenteric fat infiltration more prevalent in RCD II than RCD I Scoring system construction • Multivariate analysis showed following parameters to be independently associated with RCD II: ○ Presence of less than 10 folds per 5cm jejunum ○ Diffuse bowel wall thickening ○ Mesenteric fat infiltration

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**

- At optimal cut-off from ROC analyses of 2, none of 10 patients with RCD II were missed anf absence of RCD correctly diagnosed in 15/18 patients without RCD II
- Readers disagreed for 9/40 studies on one feature
- 6/9 discrepancies occurred in patients with RCD II
- Agreement on:
  - 37/40 wall thickening
  - 37/40 mesenteric fat infiltration
  - 37/40 on <10 jejunal folds

**see below for proposed scoring system

Diagnostic accuracy of MR enteroclysis scoring system in test group
Sensitivity 100% (66 – 100), specificity 83% (58-96)

TP 10	FN 3
FP 0	TN 15

Diagnostic accuracy of MR enteroclysis scoring system in validation group
Sensitivity 87% (58 – 98), specificity 96% (78-100),

TP 13	FN 1
FP	TN

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**

	2 | 24
	
	Survival analysis and detection of CD-related malignancy
	• 14/68 patients died during follow-up
	  ○ 2/41 with MR score of <2
	  ○ 12/27 with MR score of ≥2
	  ○ Diagnosis RCD II in 13/14 of those that died
	  ○ Causes = EATL (n=8); sepsis (n=2); meningo-encephalitis (n=2); disseminated small-bowel carcinoma (n=1), malabsorption (n=1)
	• 5 year cumulative survival rate 95% in patients with MR score <2 compared with 56% in patients with an MR score ≥2

Source of funding	
Comments	

<u>Definintions</u>:
CD: diagnosed based on the results of duodenal biopsies and positive serology for antihuman tTG and EMA in all patients
Uncomplicated CD: diagnosed if during follow-up clinical symptoms and villous atrophy improved without the need for immunosuppressive therapy
RCD I: diagnosed in case of persisting villous atrophy despite a GFD, but with normal phenotype of IEL's
RCD II: diagnosed in case of persisting villous atrophy with abnormal phenotype IEL's
EATL and adenocarcinoma: histological analysis of biopsy or resection specimens, and were established according to international consensus criteria
 	
Proposed scoring system: score calculated by adding total number of points
• Number of jejunal folds per 5cm
  ○ ≥10 = 0 points
  ○ <10 = 1 point	

Bibliographic reference	**Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system** **Reference ID:**

	• Mesenteric fat infiltration
	  ○ Present = 1 point
	  ○ Absent = 0 point
	• Diffuse bowel wall thickening
	  ○ Present = 1 point
	  ○ Absent = 0 point
	
	Author conclusions: : MR enteroclysis can be used to investigate the presence of RCD II or malignancy in symptomatic patients with CD

Bibliographic reference	**Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII**
Study type and aim	Retrospective cohort study to examine the clinical and biological presentations at diagnosis of patients with RCD I and RCD II to assess the onset of overt lymphoma and predictive factors of survival
Study quality	1. Could the selection of patients have introduced bias? 2. Is there concern that the included patients do not match the review question? 3. Could the conduct or interpretation of the index test have introduced bias? 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? 5. Could the reference standard, its conduct, or its interpretation have introduced bias? 6. Is there concern that the target condition as defined by the reference standard does not match the review question? 7. Could the patient flow have introduced bias? **Overall risk of bias:**
Number of patients	N= 57 ; 14 RCD I; 43 RCD II
location	France

Bibliographic reference	Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII
Patient characteristics	**Inclusion criteria:** diagnosis of RCD **Exclusion criteria**: Patients with an incorrect diagnoses (n=11), patients with indeterminate IEL phenotype (n=9), or those that presented with celiac disease revealed by an overt T-cell lymphoma (n=6). **Mean age**: 50 **Mean age at diagnosis**: 45 **Mean years since diagnosis**:4
Signs and symptoms	Lethargy Diarrhoea – 87% Abdominal pain – 58% Weight loss – 64% Nausea and vomiting Anemia
Investigations	• Clinical data recorded • Blood tests – haemoglobin, folic acid, vitamin B12, albinum, transaminase levels. • Serologic tests – IgA and IgG AGA, IgA EMA, IgA tTG • HLA genotyping – PCR using InnoLipa tests for HLA-DRB1 and –DQB1 • Endoscopic evaluation – included upper GI endoscopy or doible balloon endoscopy with gastric and small intestinal biopsies, colonoscopy with colonic biopsy, and VCE • For histologic assessment: o Minimum of 4 gastric, duodenal, colonic biopsy specimens fixed in 10% formalin, embedded in paraffin, and sections stained with H&E. o villous atrophy assessed according to Marsh-Oberhuber o % of IEL's established on well-oriented serial sections by counting at least 500 EC's • Immunohistochemistry o Performed on sections form paraffin-embedded biopsy specimens using antibodies directed against CD3 (rabbit polyclonal antibody antihuman CD3; CD8 (mouse polyclonal antibody antihuman CD3), CD4, and

Bibliographic reference	Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII
	CD30, and on acetone-fixed frozen tissue sections using antibodies directed against CD103, Beta F1, and TCR gamma 1, and a 3 stage indirect immunoperoxidase technique. --> percentage of CD3+CD8- IEL's assessed • Flow cytometry phenotyping o IEL's and lamina propria lymphocytes isolated from duodenal biopsy specimens o Peripheral blood lymphocytes isolated on Ficoll gradient according to standard procedures o Multicolour staining of lymphocytes performed using PerCP-cyanin 5.5 labeled antiCD45, phycoerythrin-conjugated anti CD3 anti CD8 or anti-TCR abeta antibodies, fluorescein isothiocyanate-conjugated anti cd4, antiCD3, and anti TCR ygamma antibodies and analysed on s BDLSR 1 using CellQuest software • Clonal TCR by PCR o Performed on DNA extracted from intestinal, cutaneous, and bronchopulmonary frozen biopsy specimen and from mononuclear cells isolated from peripheral blood or from pleural and/or peritoneal fluids by multiplex PCR
Length of follow up	Evaluation performed at diagnosis and at regular intervals (every 6 months) during follow-up. CT and PET performed at diagnoses to rule-out lymphoma and then every 6 months or if justified by clinical symptoms
Outcome	Outcomes of histopathology, immunohistochemistry, TCR PCR and survival analyses in RCD patients
Results	• Endoscopic and histologic features o Ulcerative jejunitis in 28% RCD 1 and 67% RCD II o Large ulcerations with diameter >1cm only observed in RCD II patients o Median number of IEL's in duodenal sections 62.5 in RCD I and 85.5 in RCD II • Immunohistochemistry findings o Sensitivity and specificity to detect RCD II were both 100%, whereby RCD II patients had abnormal phenotype of >50% IEL's positive to anti CD3E but negative to anti CD8 antibodies • Flow cytometry findings o Confirmed normal phenotype in 12 RCD I and abnormal phenotype in 26 RCD II patients • TCR clonality findings o Sensitivity to detect RCD II = 91% (83 – 100)

Bibliographic reference	Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII
	○ Specificity to detect RCD II = 100% (100 – 100)
Source of funding	
Comments; none	
Definition RCD: diagnosis based on clinical relapse with persistent malabsorbtion syndrome and on histology showing persistent villous atrophy with increased numbers of IEL's after 1 year of strict adherence to GFD **Definition RCD 1**: defined by normal IEL phenotype (<25% CD103+ or CD45+ IEL's lacking surface CD3 on flow cytometry, or <50% CD3+CD8- IEL's in formol-fixed sections) and the absence of detectable clonality in duodenal biopsy specimens **Definition RCD II**: define by the following abnormal phenotype of IEL's - >25% CD103+ or CD45+ IEL's lacking surface CD3/TCR complexes on flow cytometry or >50% IEL's expressing intracellular CD3E but no CD8 in formol-fixed solutions and/or the presence of a detectable clonal TCR rearrangement in duodenal biopsy specimens	

Bibliographic reference	TEMPLATE
Study type and aim	
Study quality	8. Could the selection of patients have introduced bias? 9. Is there concern that the included patients do not match the review question? 10. Could the conduct or interpretation of the index test have introduced bias? 11. Is there concern that the index test, its conduct, or interpretation differ from the review question? 12. Could the reference standard, its conduct, or its interpretation have introduced bias? 13. Is there concern that the target condition as defined by the reference standard does not match the review question? 14. Could the patient flow have introduced bias?

Bibliographic reference	TEMPLATE
	Overall risk of bias:
Number of patients	
location	
Patient characteristics	**Inclusion criteria:** **Exclusion criteria**: **Mean age**: **Mean age at diagnosis**: **Mean years since diagnosis**:
Signs and symptoms	Lethargy Diarrhea Abdominal pain Weight loss Nausea and vomiting Anemia
Investigations	
Length of follow up	
Outcome	
Results	Primary causes of NRCD: • Incorrect CD diagnosis: • Gluten ingestion: • Microscopic colitis: • Bacterial overgrowth: • Lactose intolerance: • Inflammatory colitis • IBS:

Bibliographic reference	TEMPLATE
	• RCD Other causes: • Anorexia • Pancreatic insufficiency • Diverticular disease • Medication-induced diahorrea • Combined variable immunodeficiency • Colorectal cancer • Anorectal dysfunction • Human immunodeficiency virus
Source of funding	
Comments	

D.9 Review question 6.2

Bibliographic reference (Ref ID)	Al-tp,a et al (2006)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 2000 to 2005 **Inclusion criteria:** patients with RCDII referred to one of 2 tertiary referral centres for treatment and with aberrant T cells of 25% or more

	of intraepithelial lymphocytes **Definition of RCD:** RCDII defined as clinical relapse or persisting malabsorpotion after at least a year of strict adherence to GFD, histopathology showing at least partial villous atrophy (Marsh IIIA, B, C or ulcerative jejunitis) after excluding other causes of villous atrophy, and at least 25% or more of IELs showing aberrant T-cells on T-cell flow-cytometry. **Exclusion criteria:** Presence of enteropathy-associated T-cell lymphoma determined radiologically (small-bowel follow-through, CT scan of the thorax and abdomen; plus whole body PET scan), endoscopically (upper GI endoscopy, VCE, and/or DBE), as well as with bone marrow aspirates; history of malignant disease; serious cardiovascular disease, renal disease or active infection; abnormalities found on imaging, endoscopy, histology, and/or bone marrow examination suggestive of malignant lymphoma; haemoglobin level less than 5.0 mmmol/L, leukocyte count less than 4000 per mm3, platelet count less than 100 000 per mm3; pregnancy or women breastfeeding; serum hepatitus C virus positive, serum hepatitus B surface antigen positive, serum anti-human immunodeficiency virus positive; cyclosporin therapy in last 6 months; experimental drug within 30 days of study entry **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not described **RCD type:** II **Number of patients included:** 17 **Concomitant conditions:** not reported **Comments:** all had WHO performance status of 0-1; most patients had prednisone for months before inclusion but this was stopped before treatment with 2-CDA
Treatment	**Details:** other immunomodulatory drugs not permitted **Arm No:** 1 **Name:** cladribine (2-CDA) **N:** 17 **Pharmacological agent:** cladribine agent 1: administration: intravenous agent 1: dosage (intravenous): 0.1 Comments: patients were hospitalised before 2-CDA was given intravenously (0.1 mg/kg) - this occurred for 2 hours daily for 5 days; cotrimoxazole 960 mg (gluten-free suspension) was given orally 2 times daily and for 2 days a week at week) until 6 months after 2-CDA therapy (prophylaxis against Pneumocystis carinii pneumonia); some patients had supplemental folic acid, vitamin B12 and/or iron if indicated; those who had clinical, histologic, and/or immunologic response received an additional second course (6 patients) or a third course (7 patients)
Other	**Source of funding:** not reported

	Authors' conflicts of interest: not reported **Additional comments:** EATL diagnosis was established with WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues with large- or medium-size T-cell proliferation expression CD3+, CD8(+/-), CD103+ (all those who developed EATL had CD3+, CD8-, CD30+ large-cell lymphoma)
Notes on outcomes	**Clinical response –** defined as disappearance of diarrhoea, improvement in performance status according to WHO scale or at least 2 of the following: increase of BMI >1 point, increase albumin 10% or more from baseline, or increase in haemoglobin >1 point **serological response:** Proportion of IELs per100 epithelial cells (%) - decrease of 20% or more was considered significant

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	17		60.88 [rng 46–76][a]
Sex (n female)	Dichotomous	17	9	(52.9%)
HLA-DQ status - DQ2 homozygous	Dichotomous	17	7	(41.2%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	17	10	(58.8%)
TCDy-PCR - monoclonal	Dichotomous	17	17	(100.0%)
TCRy-PCR - polyclonal	Dichotomous	17	0	(0.0%)

a age at diagnosis of RCD

Results

		cladribine (2-CDA)		
		N	**k**	**mean**
Clinical response:				
body mass index (kg/m2) – 0d	Continuous	17		20.6 (SD 2.12)
body mass index (kg/m2) – 48d	Continuous	17		21.2 (SD 3.14)[a]
proportion achieved – 88d	Dichotomous	17	6	(35.3%)
serological response:				
mean haemoglobin (mmol/L) – 0d	Continuous	17		7.65 (SD 1.35)

	mean haemoglobin (mmol/L) – 48d	Continuous	17		7.69 (SD 1.29)*a*
	mean corpuscular volume (FL) – 0d	Continuous	17		85 (SD 6.3)
	mean corpuscular volume (FL) – 48d	Continuous	17		92 (SD 6.9)*a*
	leukocytes (x 10 exp 9 per L) – 0d	Continuous	17		7.27 (SD 1.85)
	leukocytes (x 10 exp 9 per L) – 48d	Continuous	17		7.07 (SD 1.48)*a*
	neutrophils (%) – 0d	Continuous	17		56 (SD 12)
	neutrophils (%) – 48d	Continuous	17		60 (SD 13)*a*
	lymphocytes (%) – 0d	Continuous	17		19.5 (SD 10.2)
	lymphocytes (%) – 48d	Continuous	17		21.7 (SD 7.68)*a*
	monocytes (%) – 0d	Continuous	17		7.9 (SD 5.8)
	monocytes (%) – 48d	Continuous	17		8.2 (SD 6)*a*
	platelets (x 10 exp 9 per L) – 0d	Continuous	17		334 (SD 94.9)
	platelets (x 10 exp 9 per L) – 48d	Continuous	17		296 (SD 89.5)*a*
	mean albumin level (g/L) – 0d	Continuous	17		30 (SD 7.2)
	mean albumin level (g/L) – 48d	Continuous	17		33.7 (SD 7.49)*a*
	Proportion of IELs per100 epithelial cells (%) – 0mo	Continuous	17		72.7 (SD 23.3)
	Proportion of IELs per100 epithelial cells (%) – 22mo	Continuous	17		57.7 (SD 26.9)
	histological response:				
	disappearance of ulcerative jejunitis	Dichotomous	5	5	(100.0%)
	proportion achieved improvement – 48d	Dichotomous	17	10	(58.8%)
	no response – 48d	Dichotomous	17	5	(29.4%)
	deterioration – 48d	Dichotomous	17	2	(11.8%)
	Marsh IIIC – 0mo	Dichotomous	17	6	(35.3%)
	Marsh IIIC – 22mo	Dichotomous	17	4	(23.5%)
	Marsh IIIB – 0mo	Dichotomous	17	1	(5.9%)
	Marsh IIIB – 22mo	Dichotomous	17	3	(17.6%)
	Marsh IIIA – 0mo	Dichotomous	17	5	(29.4%)

	Marsh IIIA – 22mo	Dichotomous	17	8	(47.1%)
	Marsh II – 0mo	Dichotomous	17	0	(0.0%)
	Marsh II – 22mo	Dichotomous	17	1	(5.9%)
	Marsh I – 0mo	Dichotomous	17	0	(0.0%)
	Marsh I – 22mo	Dichotomous	17	1	(5.9%)
	presence of ulcerative jejunitis – 0mo	Dichotomous	17	5	(29.4%)
	presence of ulcerative jejunitis – 22mo	Dichotomous	17	0	(0.0%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 48d	Dichotomous	17	6	(35.3%)
	deterioration (signficant increase in % aberrant IELs) – 48d	Dichotomous	17	2	(11.8%)
	Overall response:				
	Clinical, histologic and/or immunological response – 48d	Dichotomous	17	1[b]	(5.9%)
	adverse events:				
	nausea and vomiting – 88d	Dichotomous	17	3	(17.6%)
	diarrhoea – 88d	Dichotomous	17	1	(5.9%)
	bronchitis – 88d	Dichotomous	17	1	(5.9%)
	lymphopenia – 88d	Dichotomous	17	0	(0.0%)
	monocytopenia – 88d	Dichotomous	17	0	(0.0%)
	anaemia requiring transfusion – 88d	Dichotomous	17	0	(0.0%)
	survival/overall mortality:				
	overall mortality – 56d	Dichotomous	17	7[c]	(41.2%)
	overall mortality – 88d	Dichotomous	17	2[d]	(11.8%)
	a uncertain of denominator included in this outcome *b patient considered to have complete remission* *c developed EATL at start of treatment and subsequently died (mean 14 months)* *d 1 from bronchiectasis from persistent postnasal discharge in association with EATL localisation in paranasal sinuses and another from progressive refractory emanciation*				
	period is mean follow-up of 22 months (range 7 to 67 months)				

Bibliographic reference (Ref ID)	Al-Toma,A. et al. (2007)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** records from 1992 to 2005 **Inclusion criteria:** patients with complicated forms of coeliac disease at tertiary referral centre for coeliac disease **Definition of RCD:** persisting villous atrophy with crypt hyperplasia and increased IELs in spite of a GFD for more than 12 months or when severe symptoms necessitate intervention independent of the duration of the diet (RCD II - aberrant IEL population) **Exclusion criteria:** patients treated with cyclosporin or interleukin-10 **Length of time on a gluten-free diet:** more than 12 months (or severe symptoms) **Description of gluten-free diet (and how adherence was monitored):** not described; adherence to diet was checked by a dietician (in addition to clinical assessment, all patients with positivity for EMA and/or anti-tTG at time of diagnosis of CD were negative after GFD confirming strict adherence) **RCD type:** I and II (reported separately) **Number of patients included:** 93 **Concomitant conditions:** not reported **Comments:** it is possible that some patients reported in this study were also reported in Goerres 2003 (those treated between 1992 and 1998 may be included in both studies); study also included patients with primary and secondary EATL but results with these patients were not extracted; EATL was excluded in RCD patients using radiological and endoscopic methods (small bowel follow-through, CT scanning, whole-body PET, upper gastrointestinal endoscopy, VCE and/or DBE) as well as trephine bone-marrow biopsies (pre-2003: small bowel follow-through or CT scans but post-2003 also have negative PET, VCE and/or DBE); details about reason for allocation to different treatment groups not reported so unclear if groups were similar
Treatment	**Arm No:** 1 **Name:** Patients with any combination of treatments **N:** 93 **Pharmacological agent:** prednisone alone, prednisone+azathioprine,or clad

	agent 1: administration: oral Comments: includes 6 patients treated with ASCT only and 9 with partial small-intestine resection only **Arm No:** 2 **Name:** Prednisone **N:** 47 **Pharmacological agent:** prednisone agent 1: administration: oral Comments: 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response **Arm No:** 3 **Name:** Azathioprine + prednisone **N:** 46 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 2: administration (if different): oral Comments: prednisone - 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response; azathioprine at 2 mg/kg/d for 52 or more weeks **Arm No:** 4 **Name:** Azathioprine and prednisone, followed by cladribine **N:** 23 **Pharmacological agent:** azathioprine+prednisone followed by cladribine agent 1: administration: oral agent 2: administration (if different): oral agent 3: administration (if different): intravenous Comments: prednisone - 40 mg/d for 6 weeks then tapered to 10 mg/d over 6 weeks and, then tapered to 2.5-0 mg/d after 3 months, depending on response; azathioprine at 2 mg/kg/d for 52 or more weeks; cladribine - 0.1 mg/kg/d for 5 days, in 1-3 courses every 6 months, depending on response
Other	**Source of funding:** not reported **Authors' conflicts of interest:** none reported
Notes on	**n/a**

outcomes					
Baseline characteristics			**All study participants**		
			N	**k**	**mean**
	Patient characteristics:				
	Sex (n female)	Dichotomous	93	62	(66.7%)
	RCD type 1				
	Patient characteristics:				
	Age	Continuous	43		49 (SD 14)[a]
	Sex (n female)	Dichotomous	43	31	(72.1%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	34	11	(32.4%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	34	23	(67.6%)
	Proportion of IELs per100 epithelial cells (%)	Continuous	43		60 (SD 25.9)[b]
	Proportion of IELs per100 epithelial cells (%)	Continuous	50		3 (SD 1.9)*b*
	presence of ulcerative jejunitis	Dichotomous	43	0	(0.0%)
	RCD type 2				
	Patient characteristics:				
	Age	Continuous	50		59 (SD 9.5)[c]
	Sex (n female)	Dichotomous	50	31	(62.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	46	23	(50.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	46	23	(50.0%)
	a *age at diagnosis of RCD (mean 47 at diagnosis of CD)*				
	b *this does not appear to have been measured again after treatment*				
	c *age at diagnosis of RCD (mean 50 at diagnosis of CD)*				
			Azathioprine and prednisone, followed by cladribine		
			N	**k**	**mean**

	RCD type 2				
	Patient characteristics:				
	presence of ulcerative jejunitis	Dichotomous	23	5[a]	(21.7%)
	a all patients treated with cladribine had RCDII				
Results			**Patients with any combination of treatments**		
			N	**k**	**mean**
	RCD type 1				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	43		(SD 58)
	overall mortality	Dichotomous	43	3[a]	(7.0%)
	RCD type 2				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	50		96
	overall mortality	Dichotomous	50	28[b]	(56.0%)
	a due to unrelated causes: COPD, alcoholic cirrhosis, lung carcinoma *b 23 due to EATL, 4 refractory state and emaciation, 1 neurocoeliac (unclear which treatment they had except neurocoeliac was due to ASCT)*				
				Prednisone	
				N **k**	**mean**
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event		47	25%
				Azathioprine + prednisone	

			N	**k**	**mean**
	survival/overall mortality: 5-year survival (Kaplan-Meier)	Time-to-event	46		36%

			Azathioprine and prednisone, followed by cladribine		
			N	**k**	**mean**
	survival/overall mortality: 5-year survival (Kaplan-Meier)	Time-to-event	23		22%

	baseline characteristics for RCDII include 5 patients who were treated with autologous stem-cell transplantation; patients were followed-up for a mean period of 5 years (range 2 - 14) to determin transition to a more severe state (ie. to RCDII or EATL) Mean follow up was 72 montns range 24-240) for RCDI and 44 months (range 8-146) for RCDII

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

Bibliographic reference (Ref ID)	**Brar,P. et al. (2007)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** USA
Patient characteristics	**Recruitment period:** Jan 2000 to April 2005 **Inclusion criteria:** patients with coeliac disease in the university-based coeliac centre's database who were compliant but responding poorly to a GFD **Definition of RCD:** RCD type I and II definitions based on the PCR analysis for T-cell receptor gene rearrangemnet: type I showed polyclonal product and type II clonal

	Exclusion criteria: patients not compliant to GFD, bacterial overgrowth (ova and parasites detected from stool specimens, and breath tests), autoimmune enteropathy (in the presence of antijejunal antibodies) **Length of time on a gluten-free diet:** variable times (see comments) **Description of gluten-free diet (and how adherence was monitored):** Not stated; compliance was assessed by an experienced dietician. Some patients had positive EMA and/or tTG despite strict adherence for less than 12 months but all tests became negative during the study period. All patients had persistent villous atrophy and intrepithelial lymphocytosis despite the diet. **RCD type:** I and II (reported together) **Number of patients included:** 29 **Concomitant conditions:** 7 had microscopic colitis (4 responded to treatment), 6 had lymphocytic colitis and 1 had collagenous colitis (the last had moderate response to therapy) **Comments:** 1 patient was excluded from the study because they were lost to follow-up; 24 were on a GFD for at least 6 months and 5 for less than 3 months (each of these 5 required hospitalisation because of serious disease manifestations); all patients except 5 had coeliac for at least 6 months (range 1-249); patients treated with budesonide also received azathioprine or prednisone (or both) if they had more severe symptoms so groups are not comparable
Treatment	**Details:** Patients received pancreatic supplements, bismuth, and antibiotics prior to use of steroid or immunosupressants **Arm No:** 1 **Name:** Budesonide only **N:** 15 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: dosage (oral): 9 agent 1: length of treatment (mean): 6.7 agent 1: SD of treatment length: 8.5 Comments: Using Entocort EC (controlled-release budesonide); treatment length 7 months (range 1-36 months) **Arm No:** 2 **Name:** Budesonide + prednisone **N:** 3 **Pharmacological agent:** budesonide+prednisone agent 1: administration: oral agent 1: dosage (intravenous): 9

	agent 1: length of treatment (mean): 6.7 agent 1: SD of treatment length: 8.5 agent 2: length of treatment (mean): 8.5 Comments: prednisone was given at 20 to 40 mg/day, dependent on the patient (efforts were made to taper the dosage as the patient responded) **Arm No:** 3 **Name:** azathioprine + budesonide + prednisone **N:** 7 **Pharmacological agent:** azathioprine+budesonide+prednisone agent 1: administration: oral agent 1: dosage (oral): 50 agent 1: length of treatment (mean): 9.6 agent 2: dosage (oral): 9 agent 2: length of treatment (mean): 6.7 agent 2: SD of treatment length: 8.5 agent 3: length of treatment (mean): 9.6Comments: 3 patients received 75 mg/day of azathioprine (but it was not clear which other treatments these patients were receiving); prednisone was given at 20 to 40 mg/day, dependent on the patient (efforts were made to taper the dosage as the patient responded) **Arm No:** 4 **Name:** budesonide + azathioprine **N:** 4 **Pharmacological agent:** azathioprine+budesonide agent 1: administration: oral agent 1: dosage (oral): 50 agent 1: length of treatment (mean): 9.6 agent 2: dosage (oral): 9 agent 2: length of treatment (mean): 6.7 Comments: 3 patients received 75 mg/day of azathioprine (but it was not clear which other treatments these patients were receiving) **Arm No:** 5 **Name:** Budesonide on its own or with any other treatment

	N: 29 **Pharmacological agent:** budesonide with or without other therapy
Other	**Source of funding:** study reports that there were no conflicts of interest related to financial support **Authors' conflicts of interest:** study reports that there were no potential competing interests
Notes on outcomes	**Clinical response** complete (symptom resolution and no steroids) moderate (symptom resolution and steroid reduction) poor (persistent symptoms)

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	29		56.3 (SD 15.4)
Sex (n female)	Dichotomous	29	21	(72.4%)
Duration of CD (months)	Continuous	29		60.9 (SD 71.3)
positive EMA or tTGA	Dichotomous	29	31[a]	(106.9%)
negative EMA or tTG	Dichotomous	29	69	(237.9%)
primary RCD	Dichotomous	29	55	(189.7%)
secondary RCD	Dichotomous	29	45	(155.2%)
TCDy-PCR - monoclonal	Dichotomous	29	5[b]	(17.2%)
TCRy-PCR - polyclonal	Dichotomous	29	23[c]	(79.3%)
Classical presentation (diarrhoea predominant)	Dichotomous	29	90	(310.3%)
Atypical presentation (diarrhoea absent)	Dichotomous	29	10	(34.5%)
partial villous atrophy	Dichotomous	29	69	(237.9%)
total villous atrophy	Dichotomous	29	31	(106.9%)

a *authors say these patients had strict adherence and had been on the diet for less than 12 months but that all serological tests came back negative during the period of the study*

b *defined as type II refractory disease*

c defined as type I refractory disease

Results

			Budesonide only		
			N	**k**	**mean**
Clinical response:					
complete (symptom resolution and no steroids) – 7mo	Dichotomous		15	12	(80.0%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous		15	0	(0.0%)
poor (persistent symptoms) – 7mo	Dichotomous		15	3	(20.0%)

		Budesonide + prednisone		
		N	**k**	**mean**
Clinical response:				
complete (symptom resolution and no steroids) – 7mo	Dichotomous	3	1	(33.3%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	3	1	(33.3%)
poor (persistent symptoms) – 7mo	Dichotomous	3	1	(33.3%)

		azathioprine + budesonide + prednisone		
		N	**k**	**mean**
Clinical response:				
complete (symptom resolution and no steroids) – 7mo	Dichotomous	7	0	(0.0%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	7	5	(71.4%)
poor (persistent symptoms) – 7mo	Dichotomous	7	2	(28.6%)

			budesonide + azathioprine		
			N	k	mean
Clinical response:					
complete (symptom resolution and no steroids) – 7mo		Dichotomous	4	3	(75.0%)
moderate (symptom resolution and steroid reduction) – 7mo		Dichotomous	4	0	(0.0%)
poor (persistent symptoms) – 7mo		Dichotomous	4	1	(25.0%)

		Budesonide on its own or with any other treatment		
		N	k	mean
Clinical response:				
body mass index (kg/m2) – 0mo	Continuous	29		20.8 (SD 3.9)
body mass index (kg/m2) – 7mo	Continuous	29		21.1 (SD 3.6)
complete (symptom resolution and no steroids) – 7mo	Dichotomous	29	16	(55.2%)
moderate (symptom resolution and steroid reduction) – 7mo	Dichotomous	29	6	(20.7%)
poor (persistent symptoms) – 7mo	Dichotomous	29	7	(24.1%)
Survival/overall mortality:				
overall mortality – mo	Dichotomous	29	1[a]	(3.4%)
those with complete response				
Clinical response:				
bowel movements (time period unspecified) – 0mo	Continuous	16		6.3 (SD 6.6)
bowel movements (time period unspecified) – 7mo	Continuous	16		1.2 (SD 0.6)

	those with moderate response			
	Clinical response:			
	bowel movements (time period unspecified) – 0mo	Continuous	6	6.7 (SD 6.5)
	bowel movements (time period unspecified) – 7mo	Continuous	6	1.3 (SD 0.5)
	those with poor response			
	Clinical response:			
	bowel movements (time period unspecified) – 0mo	Continuous	7	5.5 (SD 2.2)
	bowel movements (time period unspecified) – 7mo	Continuous	7	5.5 (SD 2.9)
	a from sepsis and malnutrition; unclear when patient died			
	Follow-up is average 7 months (range 1-249) - all outcomes are recorded over average follow-up (duration of budesonide use is 6.7 months, SD 8.5)			

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

Bibliographic reference (Ref ID)	**Cellier,C. et al. (2000)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** France
Patient characteristics	**Recruitment period:** 1974 to 1998 **Inclusion criteria:** adults patient with severe symptomatic villous atrophy mimicking coeliac disease but refractory to a strict GFD of at least 6 months (termed 'refractory sprue' defined with Trier's criteria) with no initial evidence of overt lymphoma and were diagnosed at gastrointestinal referral centres between 1974 and 1998 **Definition of RCD:** Patients with severe symptomatic villous atrophy mimicking coeliac disease but refractory to a strict gluten-free diety and with no evidence of overt lymphoma (CD diagnosed if patients had severe (total or subtotal) small-intestinal villous atrophy associated with increased number of IEL, circulating antigliandin and/or antiendomysium IgA and/or IgG antibodies before a GFD or during periods of poor adherence (17 of 21 cases), HLADQw2 phenotype in 8 cases) **Exclusion criteria:** other causes of villous atrophy and overt intestinal lymphoma

	Length of time on a gluten-free diet: at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not stated; compliance was assessed with either a dietician or a physician in charge of the patient. **RCD type:** not reported **Number of patients included:** 21 **Concomitant conditions:** lymphocytic colitis in 4 patients, collageous colitis in 2 patients, collagenous sprue in 7 patients (some presenting features of patients included hyposplenism in 5 patients, dermatitus herpetiformis in 1) **Comments:** it is possible that some patients reported in this study were also reported in Malamut 2009 (those treated between 1992 and 1998 may be included in both studies); the study also included 20 'controls' with coeliac disease that were not refractory to GFD but these were not included as they did not have RCD
Treatment	**Arm No:** 1 **Name:** prednisolone (0.5 to 1.0 mg/kg per day) **N:** 15 **Pharmacological agent:** prednisolone agent 1: administration: oral agent 1: length of treatment (mean): 41 Comments: 0.5 to 1.0 mg/kg per day; treatment period ranged from 1 to 114 months
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported **Additional comments:** A questionnaire was sent to 56 different French gastroenterology referral centres in January 1997
Notes on outcomes	**Clinical response:** defined as regression of diarrhoea and improvement in nutritional status) extended steroid therapy to maintain improvement **Notes: phenotypical analysis of peripheral-blood lymphocytes was reported in the study but not extracted.**

Baseline characteristics			**All study participants**		
			N	**k**	**mean**
Patient characteristics:					
Age		Continuous	21		51 [rng 29–73]
Sex (n female)		Dichotomous	21	16	(76.2%)

	Duration of CD (months)	Continuous	21		
	Proportion of IELs per100 epithelial cells (%)	Continuous	19		70.947 [rng 9–98][a]
	presence of ulcerative jejunitis	Dichotomous	21	6	(28.6%)
	mesenteric lymph node cavitation	Dichotomous	21	6	(28.6%)
	clonal TCRy configuration present	Dichotomous	17	4	(23.5%)
	clonal TCRy configuration absent	Dichotomous	17	13	(76.5%)
	AGA and/or EMA IgA or IgG present	Dichotomous	21	21[b]	(100.0%)

a biopsies not available for 2 patients; these were considered to be abnormal in all but 3 (which were 30% or less)
b these were present in all but 4 before GFD and reappeared after times of less adherence to GFD

Results

		prednisolone (0.5 to 1.0 mg/kg per day)		
		N	**k**	**mean**
Clinical response:				
proportion achieved – 41mo	Dichotomous	15	11	(73.3%)
extended steroid therapy to maintain improvement – 41mo	Dichotomous	11		3
Histological response:				
complete villous recovery – 41mo	Dichotomous	14	3[a]	(21.4%)

a not all patients re-assessed

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

Bibliographic reference (Ref ID)	**Daum,S. et al. (2006)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** Germany

Patient characteristics	**Recruitment period:** 1997 to 2004 **Inclusion criteria:** patients with RCD identified from patient records at a tertiary referral centre who were treated with budesonide, with or without receiving systemtic corticosteroid treatment **Definition of RCD:** at least partial villous atrophy documented on duodenal histology with no clinical or histological response to a GFD after at least 6 months and persistent villous atrophy and clinical deteriorration requiring earlier therapeutic intervention despite a GFD. **Exclusion criteria:** other causes for villous atrophy including giardiasis and other parasitic infections (determined from negative stool tests and histology), bacterial overgrowth (determined from normal hydrogen breath test), tropical sprue (travel history to endemic countries), hypogammaglobulinemic sprue (normal serum IgA, IgG, and IgM and normal plasma cell numbers in duodenal biopsy), manifest lymphoma (no detectable tumour enlarged lymph nodes suggesting lymphoma in abdominal CT or MRT, normal lactate dehydrogenase), Crohn's disease (normal ileocolonoscopy, no histological hinting at Crohn's disease, no typically cicumscribed strictures), microscopic colitis (normal histology of the colon) and pancreatic insufficienty (normal stool chymotrypsin); inadvertent persisting gluten intake (determined by documented repeated dietary counselling including a visit with an experienced dietician) **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not stated; compliance with GFD determined/monitored through repeated dietary counselling including a visit with an experienced dietician (who excluded inadvertent persistent gluten intake) **RCD type:** I and II (reported separately) **Number of patients included:** 4 **Concomitant conditions:** not reported **Comments:** study included 9 patients - 1 had autoimmune enteropathy and another had C4 positive sprue-like intestinal T cell lymphoma so data on these patients has notbeen extracted; the study included another 3 patients with different additional treatments on top of budesonide and pre-treatment with prednisolone (one with CD25 antibodies, another with azathioprine, and a third with tacrolimus) – data from these patient was not extracted as they are essentially case reports
Treatment	**Arm No:** 1 **Name:** Budesonide + pre-treatment with prednisolone **N:** 2 **Pharmacological agent:** budesonide+prednisolone agent 1: administration: oral agent 1: average dosage (oral): 10.2 agent 1: length of treatment (mean): 24 agent 2: administration: oral agent 2: average dosage (oral): 35

	agent 2: length of treatment (mean): ? Comments: budesonide dosage ranged from 9 to 12 mg/day over 1 to 60 months; 5 patients had pre-treatment with prednisone ranged at 40 mg/d from mean 4 months (1 to 144 months); of those patients who had pre-treatment with prednisone **Arm No:** 2 **Name:** Budesonide only **N:** 2 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: average dosage (oral): 10.2 agent 1: length of treatment (mean): 24 Comments: no pre-treatment with prednisolone
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as increase of BMI by at least 10% or more OR a clinically significant decrease in bowel movements and an at least stable BMI
Baseline characteristics	

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	4		52.5 [rng 31–69]
Sex (n female)	Dichotomous	4	1	(25%)
Duration of CD (months)	Continuous	4		100 [rng 9–252]
HLA-DQ status - DQ2 homozygous	Dichotomous	4	2	(50%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	4	2	(50%)
primary RCD	Dichotomous	4	3	(75.0%)
secondary RCD	Dichotomous	4	1	(25.0%)
TCDy-PCR - monoclonal	Dichotomous	4	1[a]	(25.0%)
TCRy-PCR - polyclonal	Dichotomous	4	2[b]	(50.0%)

	TCRy-PCR - unclear	Dichotomous	4	1	(25.0%)
	RCD type 1				
	Patient characteristics:				
	Sex (n female)	Dichotomous	2	0	(0.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	2	1	(50.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	2	1	(50.0%)
	primary RCD	Dichotomous	2	1	(50.0%)
	secondary RCD	Dichotomous	2	1	(50.0%)
	RCD type 2				
	Patient characteristics:				
	Sex (n female)	Dichotomous	2	1	(50.0%)
	HLA-DQ status - DQ2 homozygous	Dichotomous	2	2	(100.0%)
	HLA-DQ status - DQ2 hetergozygous	Dichotomous	2	0	(0.0%)
	primary RCD	Dichotomous	2	0	(0.0%)
	secondary RCD	Dichotomous	2	2	(100.0%)

a authors state were positive clonality (for one patient it was not clear if they were positive or negative)
b authors state were negative clonality (for one patient it was not clear if they were positive or negative)

Results			**Budesonide + pre-treatment with prednisolone**		
			N	**k**	**mean**
	Clinical response:				
	bowel movements per day – 0mo	Continuous	2		5 [rng 2–8]
	bowel movements per day – 24mo	Continuous	2		2 [rng 1–3]
	body mass index (kg/m2) – 0mo	Continuous	2		19.7 [rng 19.6–19.8]
	body mass index (kg/m2) – 24mo	Continuous	2		21.5 [rng 21.3–21.8]
	proportion achieved	Dichotomous	2	2[a]	(100%)

serological response:				
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	1		90[b]
Proportion of IELs per100 epithelial cells (%) – 24mo (median)	Continuous	2		58.5 [rng 50–67]*b*
Histological response:				
remained at Marsh IIIC at 0mo and 24 mo	Dichotomous	1	1	
Marsh IIIA at 0mo to Marsh IIIB at 24 mo	Dichotomous	1	1	
Adverse events:				
skin fragility – 14mo	Dichotomous	2	1	(50.0%)
postprandial abdominal pain and weight loss with budesonide–	Dichotomous	2	1	(50.0%)

a *at average of 28.5 months (range21 to 36)*
b *this was not measured in one patient*

		Budesonide only		
		N	**k**	**mean**
Clinical response:				
bowel movements per day – 0mo	Continuous	2		5.5 [rng 5–6]
bowel movements per day – 24mo	Continuous	2		3.5 [rng 2–5]
body mass index (kg/m2) – 0mo	Continuous	2		20.6 [rng 18.4–22.8]
body mass index (kg/m2) – 24mo	Continuous	2		20.75 [rng 18.4–23.1]
proportion achieved	Dichotomous	2	1[a]	(50.0%)
Serological response:				
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	2		64 [rng 50–78]

	Proportion of IELs per100 epithelial cells (%) – 24mo (median)	Continuous	1		87 [b]
	Histological response:				
	Marsh IIIB at 0mo and 24 mo	Dichotomous	1 [c]	1	
	Adverse events:				
	skin fragility	Dichotomous	2	0	(0.0%)
	postprandial abdominal pain and weight loss with budesonide–	Dichotomous	2	0	(0.0%)
	a *at 28 months* *b* *this was not measured in one patient* *c* *Marsh was IIIC in one patient initially but was not measured after budesonide*				
	budesonide was taken for 24 months (range 1 to 60) across all patients.				

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

Bibliographic reference (Ref ID)	**Goerres,M.S. et al. (2003)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 1998 - 2000 **Inclusion criteria:** patients initally referred to an out-patient clinic of a tertiary referral centre for coeliac disease with RCD **Definition of RCD:** malabsorption in the presence of persisting or recurring severe inflammatory infiltration of the epithelium and lamina propria with lymphocytes, hyperplasia of crypts and/or partial, subtotal or total villous atrophy in the small intestinal mucosa despite strict adherence to a GFD for at least a year. **Exclusion criteria:** diagnosis of other possible underlying diseases, such as bacterial overgrowth, giardiasis, eosinophilic enteritis, inflammatory bowel disease, hypogammaglobulinemic sprue, primary idiopathic collagenous colitis, tropical sprue, malignancy and EATL; poor compliance to a GFD; presence of anti-endomysium antibodies and high levels of antigliandine antibodies for at least 2 months; presence of other severe pathology such as a history or presence of cancer or any other premalignant disease, severe cardiovascular disease, presence of any concurrent infection, ulcerative colitis or lymphoma; breast-feeding or pregnancy; positive serum anti-hepatitis C

	virus, serum hepatitus B surface antigen, or anti-HIV **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; compliance to GFD confirmed for inclusion with the aid of a dietician, the referring physician, the consulting GP, and the treatment team **RCD type:** I and II (reported separately) **Number of patients included:** 19 **Concomitant conditions:** a number of concomitant conditions (ie. ulcerative colitis, inflammatory bowel disease, etc) excluded **Comments:** it is possible that some patients reported in this study were also reported in Al-Toma 2007 (those treated between 1992 and 1998 may be included in both studies); all but 1 patient had more than 70% aberrant T-cells (one patient had 25%)
Treatment	**Arm No:** 1 **Name:** Azathioprine after pre-treatment with prednisone **N:** 0 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 1: length of treatment (mean): 13 agent 2: administration (if different): oral Comments: at least 52 weeks of treatment; 2 mg/kg/day of azathioprine; prednisone was started at 40 mg/d for 6 weks and tapered to 10 mg/d after 6 weeks and, if possible, 2.5-0 mg/d after 3 months (depending on the clinical condition and biochemical parameters of the patient)
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response**- defined as diappearance of diarrhoea, or loss of fatigue or weakness **Serological response:** decrease in intraepithelial lymphocytosis - not clear how this was defined (ie. what was considered a decrease) **Histological response –** 'improved' defined as improvement of small intestinal histology which may or may not have had a decrease of intra-epithelial lymphocytosis **survival/overall mortality** overall mortality - there is some inconsistency in the study between the patient IDs in the table and the text which appears to report on 19 patients. The information from the table in the study was extracted into this evidence table.
Baseline characteristics	**All study participants**

			N	k	mean
	RCD type 1				
	Patient characteristics:				
	Age	Continuous	10		58.5 (SD 12.7)[a]
	Sex (n female)	Dichotomous	10	8	(80.0%)
	TCDy-PCR - monoclonal	Dichotomous	9	0	(0.0%)
	TCRy-PCR - polyclonal	Dichotomous	9	6	(66.7%)
	TCRy-PCR - unknown	Dichotomous	9	3[b]	(33.3%)
	HLA-DQ - D2	Dichotomous	10	8	(80.0%)
	HLA-DQ - DQ2 negative	Dichotomous	10	1	(10.0%)
	HLA-DQ - D8	Dichotomous	10	1	(10.0%)
	RCD type 2				
	Patient characteristics:				
	Age	Continuous	8		57 (SD 9.9)*a*
	Sex (n female)	Dichotomous	8	7	(87.5%)
	TCDy-PCR - monoclonal	Dichotomous	7	4	(57.1%)
	TCRy-PCR - polyclonal	Dichotomous	7	2	(28.6%)
	TCRy-PCR - unknown	Dichotomous	7	1*b*	(14.3%)
	HLA-DQ - D2	Dichotomous	8	8	(100.0%)
	HLA-DQ - DQ2 negative	Dichotomous	8	0	(0.0%)
	HLA-DQ - D8	Dichotomous	8	0	(0.0%)
	a *age at treatment* *b* *reported to be 'weak clonal'*				

		Azathioprine after pre-treatment with prednisone		
Results		**N**	**k**	**mean**

Clinical response:					
proportion achieved – 52wk	Dichotomous	18	17[a]		(94.4%)
histological response:					
Marsh IIIC – 0wk	Dichotomous	18	4		(22.2%)
Marsh IIIC – 52wk	Dichotomous	15	1		(6.7%)
Marsh IIIB – 0wk	Dichotomous	18	9		(50.0%)
Marsh IIIB – 52wk	Dichotomous	15	4		(26.7%)
Marsh IIIA – 0wk	Dichotomous	18	4		(22.2%)
Marsh IIIA – 52wk	Dichotomous	15	5		(33.3%)
Marsh II – 0wk	Dichotomous	18	1		(5.6%)
Marsh II – 52wk	Dichotomous	15	2		(13.3%)
Marsh I – 0wk	Dichotomous	18	0		(0.0%)
Marsh I – 52wk	Dichotomous	15	1		(6.7%)
survival/overall mortality:					
overall mortality – 52wk	Dichotomous	18	7		(38.9%)
Development of cancer:					
EATL	Dichotomous	18	6		(33.3%)
RCD type 1					
Clinical response:					
body mass index (kg/m2) – 0wk	Continuous	10			20.2 [rng 17–23.4]
body mass index (kg/m2) – 52wk	Continuous	10			21.5 [rng 14.5–27.1]
body weight (kg) – 0wk	Continuous	10			58.5 [rng 46–70]
body weight (kg) – 52wk	Continuous	10			62.4 [rng 43–76]
proportion achieved – 52wk	Dichotomous	10	10*a*		(100.0%)
serological response:					
mean haemoglobin (mmol/L) – 0wk	Continuous	10			12.7 [rng 10.9–13.5]
mean haemoglobin (mmol/L) – 52wk	Continuous	10			13.4 [rng 9.1–14.3]

	mean albumin level (g/L) – 0wk	Continuous	10		38 [rng 33–47]
	mean albumin level (g/L) – 52wk	Continuous	10		39 [rng 37–44]
	decrease in intraepithelial lymphocytosis – 52wk	Dichotomous	10	8	(80.0%)
	histological response:				
	proportion achieved improvement – 52wk	Dichotomous	10	[b]	8
	Marsh IIIC – 0wk	Dichotomous	10	3	(30.0%)
	Marsh IIIC – 52wk	Dichotomous	10	1	(10.0%)
	Marsh IIIB – 0wk	Dichotomous	10	5	(50.0%)
	Marsh IIIB – 52wk	Dichotomous	10	2	(20.0%)
	Marsh IIIA – 0wk	Dichotomous	10	2	(20.0%)
	Marsh IIIA – 52wk	Dichotomous	10	3	(30.0%)
	Marsh II – 0wk	Dichotomous	10	0	(0.0%)
	Marsh II – 52wk	Dichotomous	10	3	(30.0%)
	Marsh I – 0wk	Dichotomous	10	0	(0.0%)
	Marsh I – 52wk	Dichotomous	10	1	(10.0%)
	survival/overall mortality:				
	overall mortality – 52wk	Dichotomous	10	0	(0.0%)
	Development of cancer:				
	EATL	Dichotomous	10	0	(0.0%)
	RCD type 2				
	Clinical response:				
	body mass index (kg/m2) – 0wk	Continuous	8		19.9 [rng 16.6–25.3]
	body mass index (kg/m2) – 52wk	Continuous	8		22.3 [rng 19.4–25.2]
	body weight (kg) – 0wk	Continuous	7		53.428 [rng 44–67]
	body weight (kg) – 52wk	Continuous	8		60.25 [rng 49–67]
	proportion achieved – 52wk	Dichotomous	8	7*a*	(87.5%)
	serological response:				
	mean haemoglobin (mmol/L) – 0wk	Continuous	8		11.6 [rng 10.1–13.2]

	mean haemoglobin (mmol/L) – 52wk	Continuous	8		12.2 [rng 10.5–13.8]
	mean albumin level (g/L) – 0wk	Continuous	8		30 [rng 17–43][c]
	mean albumin level (g/L) – 52wk	Continuous	8		33 [rng 31–37]
	histological response:				
	proportion achieved improvement – 52wk	Dichotomous	5	2[d]	(40.0%)
	Marsh IIIC – 0wk	Dichotomous	8	1	(12.5%)
	Marsh IIIC – 52wk	Dichotomous	5	0	(0.0%)
	Marsh IIIB – 0wk	Dichotomous	8	4	(50.0%)
	Marsh IIIB – 52wk	Dichotomous	5	2	(40.0%)
	Marsh IIIA – 0wk	Dichotomous	8	2	(25.0%)
	Marsh IIIA – 52wk	Dichotomous	5	2	(40.0%)
	Marsh II – 0wk	Dichotomous	8	1	(12.5%)
	Marsh II – 52wk	Dichotomous	5	1	(20.0%)
	Marsh I – 0wk	Dichotomous	8	0	(0.0%)
	Marsh I – 52wk	Dichotomous	5	0	(0.0%)
	survival/overall mortality:				
	overall mortality – 52wk	Dichotomous	8	7[e]	(87.5%)
	Development of cancer:				
	EATL	Dichotomous	8	6[f]	(75.0%)

a *associated with weight gain and albumin and haemoglobin increase*
b *decrease of intra-epithelial lymphocytosis in 8*
c *2 patients had very low levels and this increased dramatically in one after treatment*
d *but these patients did not have a reduction in IEL infiltration*
e *3 died before finishing 52 week treatment, others died later, most from EATL but one due to sepsis*
f *3 of these died during the treatment period*

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

Bibliographic	**Jamma,S. et al. (2011)**

reference (Ref ID)	
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** USA
Patient characteristics	**Recruitment period:** Nov 2007 to Dec 2008 **Inclusion criteria:** patients seen in clinic with RCD (with biopsy proven coeliac disease who did not respond to a GFD for at least 6 months) in whom a therapeutic trial of small intestinal release mesalamine was prescribed **Definition of RCD:** RCD type based on IEL immunohistochemistry (where CD3=CD8) - confirmed by evaluation of duodenal biopsies **Exclusion criteria:** It appears that patients underwent some testing and this may have been done to rule out other conditions (ie. all patients underwent colonoscopy for microscopic colitis so it appears this may have been an exclusion criteria, patients had breath testing for small intenstinal bacterial overgrowth, small bowel series, enterosocpy, capsule endscopy, antienterocyte antibody, cross-sectional imaging in clinical indicated); it also appears patients with other food intolerances like lactose may have been excluded **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** Not described; all patients were assessed by an expert coeliac dietician to assess for inadvertent gluten exposure and for other food intolerances such as lactose. Patients were on a GFD for a median of 24 months (range 10 to 300 months) **RCD type:** I **Number of patients included:** 10 **Concomitant conditions:** colonoscopy showed that 3 patients had lymphocytic colitis (2 treated with mesalamine and budesonide and one with mesalamine alone) and 1 had collagenous colitis (treated with both mesalamine and budesonide); 1 patien treated with mesalamine only had IgA deficiency **Comments:** those who had responded to budesonide were tapered off this drug before being treated with mesalamine but 1 patient was not able to discontinue (they were on a stable dose of 3 to 9 mg daily); those who did not respond from mesalamine were discontinued after a mean of 4.5 weeks; 3 had poly-clonal T-cell receptor, 9 had diarrhoea present (classical presentation), 7 had secondary RCD (and 3 primary)
Treatment	**Arm No:** 1 **Name:** Small intestinal release mesalamine alone **N:** 4 **Pharmacological agent:** mesalamine agent 1: administration: oral

	agent 1: average dosage (oral): 3.3 agent 1: length of treatment (mean): 22.7 Comments: one patient treated with mesalamine was previously on budesonide but did not respond to this drug; mesalamine was given in a dosage from 2 to 4 gm per day for from 3 to 53 months **Arm No:** 2 **Name:** Mesalamine + budesonide **N:** 6 **Pharmacological agent:** mesalamine+budesonide agent 1: administration: oral Comments: these patients were kept on budesonide if they had responded to the drug and were unable to taper and discontinue this medication (all were on a stable dose from 3 to 9 mg/day for at least 1 month); mesalamine was given in a dosage for 2 to 4 gm per day and budesonide from 3 to 9 mg/day **Arm No:** 3 **Name:** mesalamine with or without budesonide **N:** 10 **Pharmacological agent:** budesonide with or without other therapy agent 1: administration: oral Comments: mesalamine was given in a dosage for 2 to 4 gm per day
Other	**Source of funding:** all funding provided by the Celiac Centre at Beth Israel Deaconess Medical Centre **Authors' conflicts of interest:** no conflicts
Notes on outcomes	**Clinical response** Complete - total symptom reduction partial - at least 50% symptom reduction non-responsive - <50% symptom reduction
Baseline characteristics	

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	10		53.4

	Sex (n female)	Dichotomous	10	9	(90.0%)
	primary RCD	Dichotomous	10	3	(30.0%)
	secondary RCD	Dichotomous	10	7	(70.0%)
	Classical presentation (diarrhoea predominant)	Dichotomous	10	9	(90.0%)
	Atypical presentation (diarrhoea absent)	Dichotomous	10	1	(10.0%)
	Marsh IIIA	Dichotomous	10	5[a]	(50.0%)
	Marsh IIIB	Dichotomous	10	1*a*	(10.0%)
	Marsh IIIC	Dichotomous	10	4*a*	(40.0%)

a *this does not appear to have been re-assessed after treatment*

Results

		Small intestinal release mesalamine alone		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	4	3	(75.0%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	4	0	(0.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	4	1	(25.0%)

		Mesalamine + budesonide		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	6	2[a]	(33.3%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	6	1[b]	(16.7%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	6	3	(50.0%)

a *or if symptoms remained in remission after stopping budesonide*

b *or if reduction in budesonide dose of at least 3 mg/d without symptom worsening*

		mesalamine with or without budesonide		
		N	**k**	**mean**
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	10	5[a]	(50.0%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	10	1*a*	(10.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	10	4*a*	(40.0%)
adverse events:				
overall adverse events – 65wk	Dichotomous	10	1[b]	(10.0%)
primary lack of response to GFD				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	3	1*a*	(33.3%)
secondary lack of response to GFD				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	7	4*a*	(57.1%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	7	0*a*	(0.0%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	7	3*a*	(42.9%)
classic presentation (diarrhoea)				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	9	4*a*	(44.4%)
partial (at least 50% symptom reduction) – 65wk	Dichotomous	9	1*a*	(11.1%)
non-responsive (<50% symptom reduction) – 65wk	Dichotomous	9	4*a*	(44.4%)
atypical presentation (no diarrhoea)				
Clinical response:				
Complete (total symptom reduction) – 65wk	Dichotomous	1	1*a*	(100.0%)

	partial (at least 50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	Marsh IIIA				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	5	3[c]	(60.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	5	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	5	2*d*	(40.0%)
	Marsh IIIB				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	1	1*a*	(100.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	1	0*a*	(0.0%)
	Marsh IIIC				
	Clinical response:				
	Complete (total symptom reduction) – 65wk	Dichotomous	4	2*a*	(50.0%)
	partial (at least 50% symptom reduction) – 65wk	Dichotomous	4	0*a*	(0.0%)
	non-responsive (<50% symptom reduction) – 65wk	Dichotomous	4	2*a*	(50.0%)
	a *calculated from percentage* *b* *one had headache leading to withdrawal* *c* *approximated to nearest integer (percentages only presented in text)* *d* *calculated from percentage; approximated to nearest integer (percentages only presented in text)*				
	Average follow-up was 65.3 weeks ranging from 39 to 95 weeks (responders were followed for an average of 67.2 weeks from 39 to 95 weeks and non-responderrs discontinued after 3 to 6 weeks but were followed for an average of 62.5 weeks from 44 to 80 weeks); one patient discontinued due to headache (despite complete response) - she started mesalamine after the headache subsided but it returned so she discontinued again (not clear if this patient was also being treated with budesonide) - no other patients had side effects				

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

Bibliographic	**Malamut,G. et al. (2009)**

reference (Ref ID)	
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** France
Patient characteristics	**Recruitment period:** 1992 to 2007 **Inclusion criteria:** patients treated at 1 of 6 large hospitals in France for RCD **Definition of RCD:** Clinical relapse (chronic diarrhoea and/or severe abdominal pain) with persisten malabsorption syndrome (decreased serum leves of iron, folate, vitamin B12, and/or calcium) and on histology showing persistent villous atrophy with increased numbers of IELs after 1 year of strict adherence to a GFD. (RCDI - normal IEL phenotype with < 25% CD103+ or CD45+ IELs lacking surface CD3 on flow cytometry or < 50% CD3+CD8-IELs AND the absence of detectable clonality in duodenal biopsy speciments; RCDII - abnomal phenotypes of IELs such as > 25% CD103+ or CD45+ IELS lacking surfac CD3/TCR complexes on flow cytometry or > 50% IELs expressing intracellular CD3 but no CD8 AND/OR presence of a detectable clonal TCR rearrangement in duodenal biopsy specimens) **Exclusion criteria:** primary hypogammaglobulinemia, collageous sprue, autoimmune enteropathy and lamina propria CD4+ T-cell or CD9+ small T-cell lymphomas, indeterminate RCD because of unknown IEL phenotype, coeliac disease revealed by overt lymphoma **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** I and II (reported separately) **Number of patients included:** 57 **Concomitant conditions:** a number of concomitant conditions were excluded; 1 patient with RCD1 andf 19 with RCDII had lymphocytic gastritis, 4 with RCDI and 14 with RCDII had lymphocytic colitis **Comments:** it is possible that some patients reported in this study were also reported in Cellier 2000 (those treated between 1992 and 1998 may be included in both studies)
Treatment	**Arm No:** 1 **Name:** Corticosteroids **N:** 42 **Pharmacological agent:** corticosteroids agent 1: administration: not reported Comments: dosage not reported

	Arm No: 2 **Name:** Azathioprine **N:** 6 **Pharmacological agent:** azathioprine agent 1: administration: not reported Comments: dosage not reported **Arm No:** 3 **Name:** Methotrexate **N:** 8 **Pharmacological agent:** methotrexate agent 1: administration: not reported Comments: dosage not reported **Arm No:** 4 **Name:** Anti-tumor necrosis factor alpha **N:** 4 **Pharmacological agent:** Anti-tumor necrosis factor alpha agent 1: administration: not reported Comments: dosage not reported **Arm No:** 5 **Name:** Cyclosporin **N:** 2 **Pharmacological agent:** cyclosporin agent 1: administration: not reported Comments: dosage not reported **Arm No:** 6 **Name:** Cladribine **N:** 2 **Pharmacological agent:** cladribine agent 1: administration: not reported

	Comments: dosage not reported **Arm No:** 7 **Name:** All treated patients **N:** 57 **Pharmacological agent:** any treatment agent 1: administration: not reported Comments: dosages not reported **Comments:** authors also state that fludarabine, imatinib, cyclophosphamide-doxorubicin-etopside-steroids, mechlorethamine and bexarotene were all attempted but had no therapeutic effect; authors also report results from alemtuzumab but these results were not extracted as this drug is not licensed in the UK
Other	**Source of funding:** supported by Lymphocoeliaque, Institut National du Cancer **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as reduction in diarrhoea with a decrease of 50% of the number of stools or of weight stools per day and/or the recovering of 50% of weight loss **Histological response** complete villous recovery - if villous architecture was restored to normal partial histological response - if villous architecture improvement by at least one grade

Baseline characteristics

		All study participants		
		N	**k**	**mean**
RCD type 1				
Patient characteristics:				
Age (median)	Continuous	14		41.6[a]
Sex (n female)	Dichotomous	14	11	(78.6%)
one or more positive serology test	Dichotomous	14	4	(28.6%)
Proportion of IELs per100 epithelial cells (%)	Continuous	14		66.9
body mass index (kg/m2)	Continuous	14		18.8 (SD 2.7)
partial villous atrophy	Dichotomous	14	4[b]	(28.6%)

	total villous atrophy	Dichotomous	14	5*b*	(35.7%)
	presence of ulcerative jejunitis	Dichotomous	14	4[c]	(28.6%)
	HLA-DQ2	Dichotomous	11	10	(90.9%)
	HLA-DQ8	Dichotomous	10	1	(10.0%)
	HLA-DQ2/DQ2	Dichotomous	10	4	(40.0%)
	HLA-DQ status - DQ2/8	Dichotomous	10	0	(0.0%)
	anaemia	Dichotomous	12	6	(50.0%)
	dermatis herpetiformis	Dichotomous	14	0	(0.0%)
	autoimmune diseases	Dichotomous	14	2	(14.3%)
	liver dysfunction (chronic cytolysis)	Dichotomous	14	8	(57.1%)
	diarrhoea	Dichotomous	14	12	(85.7%)
	abdominal pain	Dichotomous	14	9	(64.3%)
	proportion with low albuminemia (< 35 g/L)	Dichotomous	11	6	(54.5%)
	unexplained liver dysfunction	Dichotomous	8	4	(50.0%)
	viral hepatitis	Dichotomous	8	3	(37.5%)
	other identified cause of liver dysfunction	Dichotomous	8	1	(12.5%)
	subtotal villous atrophy	Dichotomous	14	5*b*	(35.7%)
	RCD type 2				
	Patient characteristics:				
	Age (median)	Continuous	43		49.1*a*
	Sex (n female)	Dichotomous	43	25	(58.1%)
	one or more positive serology test	Dichotomous	36	10	(27.8%)
	Proportion of IELs per100 epithelial cells (%)	Continuous	43		91.5
	body mass index (kg/m2)	Continuous	43		17.8 (SD 1.6)
	partial villous atrophy	Dichotomous	41	9*b*	(22.0%)
	total villous atrophy	Dichotomous	41	14*b*	(34.1%)
	presence of ulcerative jejunitis	Dichotomous	43	29[d]	(67.4%)
	HLA-DQ2	Dichotomous	26	26	(100.0%)

	HLA-DQ8	Dichotomous	24	3	(12.5%)
	HLA-DQ2/DQ2	Dichotomous	24	16	(66.7%)
	HLA-DQ status - DQ2/8	Dichotomous	24	3	(12.5%)
	anaemia	Dichotomous	41	32	(78.0%)
	dermatis herpetiformis	Dichotomous	43	4	(9.3%)
	autoimmune diseases	Dichotomous	43	13	(30.2%)
	liver dysfunction (chronic cytolysis)	Dichotomous	43	21	(48.8%)
	diarrhoea	Dichotomous	43	38	(88.4%)
	abdominal pain	Dichotomous	43	23	(53.5%)
	proportion with low albuminemia (< 35 g/L)	Dichotomous	41	38	(92.7%)
	unexplained liver dysfunction	Dichotomous	21	13	(61.9%)
	viral hepatitis	Dichotomous	21	4	(19.0%)
	other identified cause of liver dysfunction	Dichotomous	21	4	(19.0%)
	subtotal villous atrophy	Dichotomous	41	18*b*	(43.9%)

a *age at diagnosis of RCD*
b *detected by upper endoscopy*
c *detected by upper endoscopy; none were greater than 1cm*
d *detected by upper endoscopy; all were greater than 1cm*

Results			**Corticosteroids**		
			N	**k**	**mean**
	RCD type 1				
	Clinical response:				
	proportion achieved	Dichotomous	10	9	(90.0%)
	histological response:				
	complete villous recovery – mo	Dichotomous	10	4	(40.0%)
	partial histological response	Dichotomous	10	0	(0.0%)

adverse events:				
drug dependency	Dichotomous	10	8	(80.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	30	23	(76.7%)
histological response:				
complete villous recovery – mo	Dichotomous	30	3	(10.0%)
partial histological response	Dichotomous	30	7	(23.3%)
adverse events:				
drug dependency	Dichotomous	31	23	(74.2%)

		Azathioprine		
		N	**k**	**mean**
RCD type 1				
Clinical response:				
proportion achieved	Dichotomous	1	1	(100.0%)
histological response:				
complete villous recovery – mo	Dichotomous	1	0	(0.0%)
partial histological response	Dichotomous	1	0	(0.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	4	2	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	4	0	(0.0%)
partial histological response	Dichotomous	4	0	(0.0%)

			Methotrexate		
			N	k	mean
RCD type 2					
Clinical response:					
proportion achieved		Dichotomous	7	5	(71.4%)
histological response:					
complete villous recovery – mo		Dichotomous	7	0	(0.0%)
partial histological response		Dichotomous	7	2	(28.6%)

		Anti-tumor necrosis factor alpha		
		N	k	mean
RCD type 1				
Clinical response:				
proportion achieved	Dichotomous	1	1	(100.0%)
histological response:				
complete villous recovery – mo	Dichotomous	1	0	(0.0%)
partial histological response	Dichotomous	1	0	(0.0%)
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	3	2	(66.7%)
histological response:				
complete villous recovery – mo	Dichotomous	3	0	(0.0%)
partial histological response	Dichotomous	3	1	(33.3%)

		Cyclosporin		
		N	**k**	**mean**
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	2	1	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	2	0	(0.0%)
partial histological response	Dichotomous	2	0	(0.0%)

		Cladribine		
		N	**k**	**mean**
RCD type 2				
Clinical response:				
proportion achieved	Dichotomous	2	1	(50.0%)
histological response:				
complete villous recovery – mo	Dichotomous	2	0	(0.0%)
partial histological response	Dichotomous	2	1	(50.0%)
Development of cancer:				
Overt lymphoma	Dichotomous	2	2[a]	(100.0%)

a occurred just after the 3rd cycle and at 2 months

		All treated patients		
		N	**k**	**mean**

	survival/overall mortality:				
	overall mortality	Dichotomous	57	29	(50.9%)
	overall mortality in those with overt lymphoma	Dichotomous	18	16[a]	(88.9%)
	RCD type 1				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	14		92.9
	overall mortality	Dichotomous	14	3[b]	(21.4%)
	overall mortality in those with overt lymphoma	Dichotomous	2	1[c]	(50.0%)
	Development of cancer:				
	Overt lymphoma	Dichotomous	14	2[d]	(14.3%)
	5-year development of overt lymphoma (Kaplan-Meier)	Time-to-event	14		14.3
	RCD type 2				
	survival/overall mortality:				
	5-year survival (Kaplan-Meier)	Time-to-event	43		43.9
	overall mortality	Dichotomous	43	26[e]	(60.5%)
	overall mortality in those with overt lymphoma	Dichotomous	16	15*c*	(93.8%)
	Development of cancer:				
	Overt lymphoma	Dichotomous	43	16[f]	(37.2%)
	5-year development of overt lymphoma (Kaplan-Meier)	Time-to-event	43		32.6
	a after median of 11.5 months *b over lymphoma progression with sepsis and malnutrition (n=1), and malnutrition (n=2)* *c after median of 11.5 months (overall for RCDI and II)* *d treatment of these 2 patients not reported; none had received immunosuppressants* *e tumoural progression and malnutrition (n=9), infections (n=4), intestinal haemorrhage (n=3), lethal thrombosis (n=2), and 1 each of oesophageal bleeding from portal hypertension & hep C and pulmonary embolism* *f 2 of these patients had cladribine and 1 had alemtuzumab; 6 had not received immunosuppressants*				
	reported follow-up periods are mean duration of treatment except for cladribine and anti-tnf alpha which were administered in cycles; none of the treatments attempted in patients with RCDII had any significant or durable effect on the number of abnomral IELS; authors also state				

	that fludarabine, imatinib, cyclophosphamide-doxorubicin-etopside-steroids, mechlorethamine and bexarotene were all attempted but had no therapeutic effect; a univariate analysis showed that abnormal IEL phenotype and increase in age at diagnosis of RCD were predictive risk factors for overt lymphoma and that abnormal IEL phenotype, clonality, and onset of overt lymphoma were predictive factors for short survival (multi-variate analysis showed that only abnormal IEL phenotype and onset of overt lymphoma were predictive of short survival)

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

Bibliographic reference (Ref ID)	**Maurino,E. et al. (2002)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective **Consecutive patients:** Yes **Country:** Argentina
Patient characteristics	**Recruitment period:** Oct 1998 to July 2000 **Inclusion criteria:** patients with a previous diagnosis of refractory sprue or if they were diagnosed with coeliac-like enteropathy and had proven lack of clinical and/or histological response to a GFD and steroids, and/or if they required high doses of steroids to maintain their clinical status. **Definition of RCD:** Refractory sprue was defined based on presence of severe enteropathy refractory to conventional therapeutic measures. All patients had severe malabsorption and requiring intensive treatment. **Exclusion criteria:** recent or current infections, high suspicion or diagnosis of lymphoma, pregnancy or low white blood cell count (< 3000 cells/mm3); other causes of villous atrophy and other malignancies also appear to have been excluded (from small bowel double-contrast radiological exam - n=7, push enteroscopy and multiple biopsies - n=4, CT - n=7, and laparotomy n=6), **Length of time on a gluten-free diet:** not reported **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** not reported **Number of patients included:** 7 **Concomitant conditions:** unclear (some excluded) **Comments:** these patients were among those included in Maurino 2006 at a longer follow-up but this study has been included because Maurino did not report outcomes by different treatments received; 5 patients were treated inpatient and 2 outpatient; duration of symptoms is median with range 3-54 months; 4 of the 5 patients that finished the trial had monoclonal T-cell receptor alpha gene rearrangement
Treatment	**Details:** Treatment period 1 year only (patients stopped receiving treatment after this time but were observed)

	Arm No: 1 **Name:** azathioprine **N:** 5 **Pharmacological agent:** azathioprine agent 1: administration: oral Comments: 1 patient started steroids in addition to azathioprine after developing sepsis from a small intesntinal perforation after laparatomy
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Notes: Change in fecal alpha 1-antitrypsin clearance and phenotypical analysis of the epithelium and lamina propria were reported in the study but not extracted.**

Baseline characteristics

		All study participants		
		N	k	mean
Patient characteristics:				
Age (median)	Continuous	7		41 [rng 28–56]
Sex (n female)	Dichotomous	7	5	(71.4%)
Duration of CD (months)	Continuous	7		48
positive IgA EMA	Dichotomous	7	2	(28.6%)
negative IgA EMA	Dichotomous	7	5	(71.4%)
iTG (U A/ml)	Continuous	7		23.42857 [rng 2–98]
IgA antiglaidin antibodies (IU/ml)	Continuous	7		31.2 [rng 2–147]
IgG antiglaidin antibodies (IU/ml)	Continuous	7		47.14 [rng 17–105]
TCDy-PCR - monoclonal	Dichotomous	7	5	(71.4%)
TCRy-PCR - polyclonal	Dichotomous	7	2	(28.6%)
presence of ulcerative jejunitis	Dichotomous	7	5	(71.4%)
jejunal stenosis	Dichotomous	7	1[a]	(14.3%)
jejunal ulcers	Dichotomous	5	3	(60.0%)

	mesenteric lymph node cavitation	Dichotomous	7	1	(14.3%)
	a patient also had ulcers on surgical macroscopic examination				

Results			azathioprine		
			N	k	mean
	Clinical response:				
	body mass index (kg/m2) – 0mo (median)	Continuous	5		17 [rng 12–21]
	body mass index (kg/m2) – 12mo (median)	Continuous	5		26 [rng 19–30]
	proportion with diarrhoea – 0mo	Dichotomous	5	4	(80.0%)
	proportion with diarrhoea – 12mo	Dichotomous	5	0	(0.0%)
	proportion with abdominal pain – 0mo	Dichotomous	5	5	(100.0%)
	proportion with abdominal pain – 12mo	Dichotomous	5	0	(0.0%)
	proportion with fever – 0mo	Dichotomous	5	2	(40.0%)
	proportion with fever – 12mo	Dichotomous	5	0	(0.0%)
	body weight (kg) – 0mo (median)	Continuous	5		46 [rng 42–54]
	body weight (kg) – 12mo (median)	Continuous	5		60 [rng 49–77]
	serological response:				
	mean haemoglobin (mmol/L) – 0mo (median)	Continuous	5		10 [rng 8–12]
	mean haemoglobin (mmol/L) – 12mo (median)	Continuous	5		13 [rng 12–14]
	mean albumin level (g/L) – 0mo (median)	Continuous	5		2 [rng 1–3]
	mean albumin level (g/L) – 12mo (median)	Continuous	5		4 [rng 3–4]
	Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	5		48 [rng 12–55][a]
	Proportion of IELs per100 epithelial cells (%) – 12mo (median)	Continuous	5		12 [rng 7–16]
	EMA positive – 0mo	Dichotomous	5	2	(40.0%)
	EMA positive – 12mo	Dichotomous	5	0	(0.0%)
	Anti-tTG antibodies negative – 0mo	Dichotomous	5	2	(40.0%)
	Anti-tTG antibodies negative – 12mo	Dichotomous	5	0	(0.0%)

	histological response:				
	Marsh III (not otherwise specified) – 0mo	Dichotomous	7	1	(14.3%)
	Marsh III (not otherwise specified) – 12mo	Dichotomous	5	0	(0.0%)
	Marsh IIIC – 0mo	Dichotomous	7	4	(57.1%)
	Marsh IIIC – 12mo	Dichotomous	5	0	(0.0%)
	Marsh IIIB – 0mo	Dichotomous	7	2	(28.6%)
	Marsh IIIB – 12mo	Dichotomous	5	0	(0.0%)
	Marsh II – 0mo	Dichotomous	7	0	(0.0%)
	Marsh II – 12mo	Dichotomous	5	2	(40.0%)
	Marsh 0 – 0mo	Dichotomous	7	0	(0.0%)
	Marsh 0 – 12mo	Dichotomous	5	3	(60.0%)
	adverse events:				
	leukopenia and maxillary and ethmoidal sinus infection – 7mo	Dichotomous	5	1[b]	(20.0%)
	pneumonia – 4mo	Dichotomous	5	1[c]	(20.0%)
	sepsis after small intestinal perforation from laparotomy – mo	Dichotomous	5	1[d]	(20.0%)
	super mesenteric artery infarction – 14mo	Dichotomous	5	1[e]	(20.0%)
	survival/overall mortality:				
	overall mortality – 12mo	Dichotomous	5	3[f]	(60.0%)
	Development of cancer:				
	EATL – 23mo	Dichotomous	5	0[g]	(0.0%)

a unclear of actual value since text says 38% and table says 48% (authors say most had intraepithelial lymphocytosis)
b patient withdrew and then died of sepsis 2 months later
c successfully treated but died due to opportunistic infection (ventricular fibrillation)
d unclear of timing; patient started on steroids and azathioprine according to protocol
e occurred 2 months after trial completed; resulted in death
f 3 patients with adverse events: one with pneumonia after 10 months, one with leukopenia after 9 month, and the other from super mesenteric artery infarction after 14 months
g after end of trial with mean 11 month follow-up after trial (range 4 to 16 m)

	All 4 patients who completed the 1 year trial experienced improvement of their condition; once these patients were no longer being treated with azathioprine (after the 1 year), all but the one patient who died of superior mesenteric artery continued to be in good health on a GFD only after the end of the trial (mean 11 months after the trial, range 4 to 16 months) with no evidence of lymphoma

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

Bibliographic reference (Ref ID)	**Peters,T.J. et al. (1978)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** unclear **Consecutive patients:** unclear **Country:** UK
Patient characteristics	**Recruitment period:** not reported **Inclusion criteria:** patients with non-responsive coeliac disease who had received a GFD **Definition of RCD:** authors just report non-responsive coeliac disease and this is those who have not responded to a GFD **Exclusion criteria:** not reported **Length of time on a gluten-free diet:** at least 3 years **Description of gluten-free diet (and how adherence was monitored):** not reported **RCD type:** not reported **Number of patients included:** 5 **Concomitant conditions:** - **Comments:** the purpose of the study was to perform analytical subcellular fractionation and enzymic microassay to examine the pathology of patients non-responsive and compare this with those who do respond to a GFD
Treatment	**Details:** - **Arm No:** 1 **Name:** Prednisolone **N:** 5 **Pharmacological agent:** prednisolone agent 1: administration: oral agent 1: dosage (oral): 20

	agent 1: length of treatment (mean): 1.6 Comments: Patient received treatment for 5, 5, 6, 9, and 7 weeks, respectively
Other	**Source of funding:** Medical Research Council and The Wellcome Trust **Authors' conflicts of interest:** not reported
Outcomes	**Notes: only outcomes relevant to this review question were extracted (results from analytical subcellular fractionation and enzymic microassay were not extracted)**

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	5		54.8 [rng 31–72]
Sex (n female)	Dichotomous	5	3	(60.0%)
primary RCD	Dichotomous	5	1	(20.0%)
secondary RCD	Dichotomous	5	4	(80.0%)

Results

		Prednisolone		
		N	**k**	**mean**
histological response:				
subtotal villous atrophy – 0wk	Dichotomous	5	5	(100.0%)
subtotal villous atrophy – 6wk	Dichotomous	5	0	(0.0%)
partial villous atrophy – 0wk	Dichotomous	5	0	(0.0%)
partial villous atrophy – 6wk	Dichotomous	5	4	(80.0%)
normal histology – 0wk	Dichotomous	5	0	(0.0%)
normal histology – 6wk	Dichotomous	5	1	(20.0%)

	follow-up recorded is average (patients were treated for 5, 5, 6, 9, and 7 weeks, respectively)

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

Bibliographic reference (Ref ID)	Rubio-Tapia,Alberto et al. (2009)
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** unclear **Country:** USA
Patient characteristics	**Recruitment period:** June 1998 to October 2007 **Inclusion criteria:** patients with RCD treated at the Mayo Clinic Rochester in the specified recruitment period **Definition of RCD:** recurrence or persistence of symptoms (diarrhoea, involuntary loss of weight and/or abdominal pain) and intestinal damage (at least partial villous atrophy) who needed alternative therapy because of a lack of response to a GFD for at least 6 to 12 months, and EMA or tTGA autoantibodies (positive to indicate CD diagnosis and negative to support GFD compliance and that patients were refractory) (RCDI/RCDII determined by absence or presence of aberrant monoclonal phenotype of IEL determined by immunohistochemical and/or T-cell clonality analyses) (previous diagnosis of CD was biopsy-proven with history of clinical response to GFD, positive serologic coeliac tests, presence of HLA alleles at risk of CD DQ2 or DQ8, family history of CD were all considered supportive for diagnosis of CD, especially patients with primary non-response to GFD) **Exclusion criteria:** other causes of nonresponsive CD inccluding dietary inquiry to exclude intentional or inadvertent gluten contamination, overt intestinal or systemic lymphoma, presence of anti-enterocyte antibodies, diagnosis of EATL prior to CD, other refractory sprue-like conditions such as adult autoimmune enteropathy, hypogammaglobulinemia sprue, collageous sprue, tropical sprue **Length of time on a gluten-free diet:** at least 6 months **Description of gluten-free diet (and how adherence was monitored):** not reported; there was a dietary inquiry to exclude intentional or inadvertent gluten contamination **RCD type:** I and II (reported separately) **Number of patients included:** 57 **Concomitant conditions:** a large number of common concomitant conditions excluded but, of all 57 patients (all but 2 treated with pharmacological treatments), 19 had microscopic colitis (17 were RCDI), and 4 had ulcerative jejunoileitis (all RCDII), and 3 had cavitating mesenteric lymphdenopathy (all RCD II);5 had small-intestine bacterial overgrowth (3 with RCDI) but diagnosis of RCD was considered only after lack of clinical response to oral antibiotics **Comments:** Purpose of study was to describe the clinical characteristics and outcome of a cohort of patients with RCD but some results

	were available about response to specific treatments - results that were reported by treatment that patients received were extracted; 2 of 57 patients did not receive any drug therapy so had parenteral nutrition alone and 1 was treated with ASCT; all patients had villous atrophy and intraepithelial lymphocytosis
Treatment	**Details:** total parenteral nutrition was given to 16 patients (12 with RCDI) and 4 required long-term home parenteral nutrition; pancreatic enzyme supplementation was used as ancillary therapy in 6 patients. **Arm No:** 1 **Name:** Prednisone **N:** 30 **Pharmacological agent:** prednisone agent 1: administration: oral Comments: 0.5 to 1 mg/kg of body weight **Arm No:** 2 **Name:** Azathioprine+prednisone **N:** 7 **Pharmacological agent:** azathioprine+prednisone agent 1: administration: oral agent 2: administration (if different): oral Comments: 0.5 to 1 mg/kg prednisone and 1-2 mg/kg per tday for azathioprine (50-150 mg/day) **Arm No:** 3 **Name:** Budesonide **N:** 15 **Pharmacological agent:** budesonide agent 1: administration: oral agent 1: dosage (oral): 9 **Arm No:** 4 **Name:** Cladribine (2-CDA) **N:** 2 **Pharmacological agent:** cladribine Comments: cladribine was 5 mg/m2day for days 1 to 5 (the paper then says 'q28 days per 2 cycles') **Arm No:** 5

	Name: All treatment groups **N:** 54 **Pharmacological agent:** any treatment
Other	**Source of funding:** National Institutes of Health grants **Authors' conflicts of interest:** none
Outcomes	**Clinical response –** defined as disappearance of diarrhoea and at least 2 of the following: increase of BMI > 1 point, increase in albumin > 10% of baseline, increase of haemoglobin > 1 point, and/or reversion > or = to 1 stage of modified Marsh classification after treatment **Clinical and histological response**: clinical response defined above and histological response defined as normal intestinal biopsy during follow-up)

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age (median)	Continuous	57		59 [rng 30–76]
Sex (n female)	Dichotomous	57	38[a]	(66.7%)
length of time on GFD (months) (median)	Continuous	57		18 [rng 12–276]
HLA-DQ status - DQ2/8	Dichotomous	57	32	(56.1%)
positive EMA or tTGA	Dichotomous	48	29[b]	(60.4%)
Marsh IIIA	Dichotomous	57	32	(56.1%)

	Marsh IIIB	Dichotomous	57	7	(12.3%)
	Marsh IIIC	Dichotomous	58	18	(31.0%)
	diarrhoea	Dichotomous	57	57	(100.0%)
	RCD type 1				
	Patient characteristics:				
	Marsh IIIA	Dichotomous	15	26	(173.3%)
	Marsh IIIB	Dichotomous	15	4	(26.7%)
	Marsh IIIC	Dichotomous	15	12	(80.0%)
	abdominal pain	Dichotomous	42	19	(45.2%)
	RCD type 2				
	Patient characteristics:				
	Marsh IIIA	Dichotomous	42	6	(14.3%)
	Marsh IIIB	Dichotomous	42	3	(7.1%)
	Marsh IIIC	Dichotomous	42	6	(14.3%)
	abdominal pain	Dichotomous	15	14	(93.3%)

a approximated to nearest integer (percentages only presented in text)
b before onset of GFD or during follow-up

			Prednisone		
			N	**k**	**mean**
Results	Overall response:				
	Clinical and histological response	Dichotomous	11	2	(18.2%)
	RCD type 2				
	serological response:				
	presence of aberrant clone	Dichotomous	6	5[a]	(83.3%)
	Development of cancer:				
	EATL	Dichotomous	6	3[b]	(50.0%)

a *uncertain of denominator as not all patients had follow-up biopsy*
b *of the 5 who had persistent clone despite treatment and 1 without aberrant clone; 18 and 24 months after clone detection*

		Azathioprine+prednisone		
		N	**k**	**mean**
Overall response: Clinical and histological response	Dichotomous	2	1	(50.0%)

		Budesonide		
		N	**k**	**mean**
Overall response: Clinical and histological response	Dichotomous	9	4	(44.4%)

		Cladribine (2-CDA)		
		N	**k**	**mean**
RCD type 2 serological response: presence of aberrant clone	Dichotomous	2	1[a]	(50.0%)

a *uncertain of denominator as not all patients had follow-up biopsy*

	All treatment groups

		N	k	mean
Clinical response:				
proportion achieved	Dichotomous	57	44[a]	(77.2%)
Overall response:				
Clinical and histological response	Dichotomous	26	9[b]	(34.6%)
survival/overall mortality:				
overall mortality	Dichotomous	57	15	(26.3%)
RCD type 1				
Overall response:				
Clinical and histological response	Dichotomous	18	6	(33.3%)
survival/overall mortality:				
5-year survival (Kaplan-Meier)	Time-to-event	15		80
overall mortality	Dichotomous	18	8[c]	(44.4%)
RCD type 2				
serological response:				
presence of aberrant clone	Dichotomous	8	5[d]	(62.5%)
Overall response:				
Clinical and histological response	Dichotomous	8	3	(37.5%)
survival/overall mortality:				
5-year survival (Kaplan-Meier)	Time-to-event	42		45
overall mortality	Dichotomous	42	7[e]	(16.7%)
Development of cancer:				
EATL	Dichotomous	42	10[f]	(23.8%)

a the numerator includes 1 patient treated with ASCT and 2 that had parenteral nutrition alone
b biopsy data only available for 26 patients; numerator may include 3 patients not treated with pharmacological treatments
c due to refractory state and emaciation in most
d in 8 of those with follow-up biopsy after median 15 months (range 7-41)

	e due to EATL in most *f after median 18 months (range 9-34)*
	Follow-up biopsies were available 23.5 months (range 6 to 54) in 26 patients; no association between subgroup (ie. RCDI or RCDII) was found after adjusting for age; 5 factors present at RCD diagnosis were found to be associated with mortality albumin (3.2 or greater g/decileter), haemoglobin 11 or more g per deciliter), age 65 or greater years, presence of aberrant IEL, and total villous atrophy (stage IIIc)

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

Bibliographic reference (Ref ID)	**Tack,G.J. et al. (2011)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** unclear **Consecutive patients:** unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** 2000 to 2010 **Inclusion criteria:** patients diagnosed with RCD II and treated with one or two courses of cladribine at the VU University Medical Centre **Definition of RCD:** based on persisting or recurring clinical symptoms and small intestinal villous atrophy after a former good response to a strict GFD (secondary RCD), despite strict adherence to the diet for more than 12 months; 20% aberrant IELs detected by flow cytometric analysis was cut-off value used to distinguish between RCD I and RCD II **Exclusion criteria:** EATL (diagnosis confirmed with WHO Classification of Tumours of Haematopoetic and Lymphoid tissues); pre-treatment with immunomodulatory drugs within 6 months or any experimental drug within 30 days not permitted (though the study appears to compare 10 who failed on pre-treatment with immunosuppressive drugs with 22 who had not previously been treated with immunosupressive drugs) **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; nutritional screening performed by a dietician who specialised in CD. **RCD type:** II **Number of patients included:** 32 **Concomitant conditions:** not reported **Comments:** includes 14 of 17 patients in Al-Toma 2006 with longer follow-up (the other 3 patients were followed up at another hospital);

	includes 10 patients who had pre-treatment with other immunosupressive drugs (azathioprine or prednisone) and reports some outcomes separately for those who did or did not receive pre-treatment
Treatment	**Arm No:** 1 **Name:** Cladribine +/- pre-treatment with azathioprine or prednisone **N:** 32 **Pharmacological agent:** cladribine with or without immunosuppression agent 1: administration: intravenous agent 1: dosage (intravenous): 0.1 Comments: Given for 5 days
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response -** defined as improvement in diarrhoea, abdominal discomfort and/or signs of malapsorption, combined with at least 2 out of the following parameters of intestinal integrity within the normal range or an improvement of 1 or more points in haemoglobin, BMI and albumin **Histological response** - complete histological remission defined as normalisation of architecture of duodenum, classified as Marsh 0 or 1 lesion according to Modified Marsh classification

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age (median)	Continuous	32		64 [rng 45–78][a]
Sex (n female)	Dichotomous	32	14	(43.8%)
Duration of CD (months)	Continuous	32		
HLA-DQ status - DQ2 homozygous	Dichotomous	32	12	(37.5%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	32	17	(53.1%)
HLA-DQ status - DQ2/8	Dichotomous	32	2	(6.3%)
HLA-DQ status - not measured/unknown	Dichotomous	32	1	(3.1%)
Proportion of IELs per100 epithelial cells (%) (median)	Continuous	32		61 [rng 21–96]

	serum albumin (g/DL) (median)	Continuous	32		36 [rng 23–47][b]
	body mass index (kg/m2) (median)	Continuous	32		21 [rng 16–27]
	haemoglobin (g/dL) (median)	Continuous	32		7.8 [rng 6–9.8]
	TCDy-PCR - monoclonal	Dichotomous	32	18	(56.3%)
	TCRy-PCR - polyclonal	Dichotomous	32	9	(28.1%)
	TCRy-PCR - unknown	Dichotomous	32	5	(15.6%)
	Marsh IIIA	Dichotomous	32	13	(40.6%)
	Marsh IIIB	Dichotomous	32	11	(34.4%)
	Marsh IIIC	Dichotomous	32	8	(25.0%)

a *at start of treatment (start of diagnosis median 64, range 42 to 78)*
b *reference value 35-52 g/L*

Results

		Cladribine +/- pre-treatment with azathioprine or prednisone		
		N	**k**	**mean**
Clinical response:				
body mass index (kg/m2) – 0mo (median)	Continuous	32		20.9 [rng 16–27]
body mass index (kg/m2) – 31mo (median)	Continuous	32		23[a]
proportion achieved – 12mo	Dichotomous	32	26	(81.3%)
proportion achieved – 24mo	Dichotomous	32	26	(81.3%)
Serological response:				
mean haemoglobin (mmol/L) – 0mo (median)	Continuous	32		7.8 [rng 6–9.8]
mean haemoglobin (mmol/L) – 31mo (median)	Continuous	32		7.9*a*
mean albumin level (g/L) – 0mo (median)	Continuous	32		36 [rng 23–47]
mean albumin level (g/L) – 31mo (median)	Continuous	32		39*a*
Proportion of IELs per100 epithelial cells (%) – 0mo (median)	Continuous	32		61 [rng 21–96]

	Proportion of IELs per100 epithelial cells (%) – 31mo (median)	Continuous	32		56*a*
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	32	3[b]	(9.4%)
	proportion achieved improvement – 12mo	Dichotomous	32	3*b*	(9.4%)
	proportion achieved improvement – 24mo	Dichotomous	32	15	(46.9%)
	proportion achieved improvement – 24mo	Dichotomous	32	15	(46.9%)
	partial remission – 24mo	Dichotomous	32	2[c]	(6.3%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	32	12*b*	(37.5%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	32	13	(40.6%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	32	8[d]	(25.0%)
	Histological, immunological and clinical response – 24mo	Dichotomous	32	13[e]	(40.6%)
	Survival/overall mortality:				
	overall mortality – 31mo	Dichotomous	32	12	(37.5%)
	death due to EATL – 31mo	Dichotomous	32	5[f]	(15.6%)
	Development of cancer:				
	EATL – 31mo	Dichotomous	32	5[g]	(15.6%)
	pre-treatment with immunosuppressive drugs				
	Clinical response:				
	proportion achieved – 12mo	Dichotomous	10	7*b*	(70.0%)
	proportion achieved – 24mo	Dichotomous	10	7*b*	(70.0%)
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion achieved improvement – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion achieved improvement – 24mo	Dichotomous	10	2*b*	(20.0%)
	proportion achieved improvement – 24mo	Dichotomous	10	2*b*	(20.0%)

	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	10	1*b*	(10.0%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	10	1*b*	(10.0%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	10	2*b*	(20.0%)
	Histological, immunological and clinical response – 24mo	Dichotomous	10	4*b*	(40.0%)
	no immunosupressive pre-treatment				
	Clinical response:				
	proportion achieved – 12mo	Dichotomous	22	21*b*	(95.5%)
	proportion achieved – 24mo	Dichotomous	22	21*b*	(95.5%)
	Histological response:				
	proportion achieved improvement – 12mo	Dichotomous	22	4*b*	(18.2%)
	proportion achieved improvement – 12mo	Dichotomous	22	4*b*	(18.2%)
	proportion achieved improvement – 24mo	Dichotomous	22	13*b*	(59.1%)
	proportion achieved improvement – 24mo	Dichotomous	22	13*b*	(59.1%)
	Immunological response:				
	proportion > or = 20% decrease in aberrant IELs – 12mo	Dichotomous	22	11*b*	(50.0%)
	proportion > or = 20% decrease in aberrant IELs – 24mo	Dichotomous	22	13*b*	(59.1%)
	Overall response:				
	Histological, immunological and clinical response – 12mo	Dichotomous	22	6*b*	(27.3%)
	Histological, immunological and clinical response – 24mo	Dichotomous	22	9*b*	(40.9%)
	responders				
	Survival/overall mortality:				
	3-year survival (Kaplan-Meier) – 36mo	Time-to-event	18		83[h]
	5-year survival (Kaplan-Meier) – 60mo	Time-to-event	18		83*h*
	overall mortality – 31mo	Dichotomous	18	3[i]	(16.7%)

	non-responders				
	Survival/overall mortality:				
	3-year survival (Kaplan-Meier) – 36mo	Time-to-event	14		63*h*
	5-year survival (Kaplan-Meier) – 60mo	Time-to-event	14		22*h*
	overall mortality – 31mo	Dichotomous	14	9[j]	(64.3%)

a *unclear of denominator*
b *approximated to nearest integer (percentages only presented in text)*
c *From marsh 3B to 2 and 3C to 3A*
d *estimated from percentage*
e *approximated to nearest integer (percentages only presented in text); however this appears different from the text which says 18 (56%) achieved this*
f *all patients who developed EATL died with a median survival of 4.4 months after diagnosis*
g *all died with a median survival of 4.4 months after diagnosis*
h *the overall median survival was 4.5 years*
i *refractory disease status (n=1), EATL (n=2)*
j *EATL (n=3), refractory disease (n=6)*

	median follow-up was 31 months (range 4 - 120 months); time to a 50% response rate was 3 years; authors report a Cox regression analysis which they state that the following values have no predictive value for response to cladribine: age at infusion, sex, TCR-gamma-clonality, percentage of averrant IELs, degree of small intestinal villous atrophy, BMI, albumin and haemoglobin (however, age was borderline not significant)

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

Bibliographic reference (Ref ID)	**Tack,G.J. et al. (2012)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Retrospective **Consecutive patients:** No **Country:** Netherlands
Patient characteristics	**Recruitment period:** June 2001 and Nov 2010 **Inclusion criteria:** all patients diagnosed with RCDI and who received tioguanine as first or second-line therapy at the Gastroenterology department of a tertiary referral centre

	Definition of RCD: diagnosis of RCD I based on persisting or recurring symptoms and small intestinal villous atrophy despite strict adherence to a GFD for at least 1 year, determined from negative serology and a specialised dietician; proportion of aberrant IELs detected with flow cytometric analysis of small intestinal biopsy had to be less than 20% **Exclusion criteria:** EATL **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** Not reported; adherence monitoring from negative serology and assessment by a specialist dietician **RCD type:** I **Number of patients included:** 12 **Concomitant conditions:** not reported **Comments:** one patient was excluded from the study due to loss of follow-up; at baseline, duodenal biopsy showed intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy in all patients; patients had weight loss and gastrointestinal symptoms including diarrhoea prior to treatment
Treatment	**Details:** study reports that four of the 10 patients who tolerated treatment for at least 6 months had been using corticosteroids at baseline (prednisone > or = 10 mg or budesonide > or = 9 mg) (all showed clinical response but only 2 showed histological response); patients were withdrawn from treatment after both clinical and complete histological response (this occurred at median 17 months) - 4 of the 6 patients withdrawn for this reaason had further endoscopic evaluation: 3 had clinical response but only 2 of these had histological response (the other evolved from Marsh I to IIIA) and one needed treatment afain after 5 months because of symptoms returning (this corresonded with developemnt of Marsh II). **Arm No:** 1 **Name:** Tioguanine **N:** 0 **Pharmacological agent:** tioguanine agent 1: administration: oral agent 1: dosage (oral): 0.36 Comments: median dosage with range 0.26 to 0.69 mg/kg corresponding to median 19 mg/day (range 18-40); administered as 18, 21 or 24 mg capsules or 20 mg tablets
Other	**Source of funding:** not reported (but paper states no funding interests) **Authors' conflicts of interest:** paper states no personal interests
Notes on outcomes	**Clinical response** – defined as amelioration of GI symptoms, combined with at least 2 of the following witih their reference range or with an improvement of 1 or more point: BMI, albumin, haemoglobin

	histological response – complete response characterised by normalisation of the small mucosal architecture as Marsh 0 or 1 (partial was improvement in Marsh by 2 or more steps) **Notes: 6-tioguanine nucleotide concentrations were reported in the study but not extracted.**

Baseline characteristics

		Tioguanine		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	12		46.6
Sex (n female)	Dichotomous	12	8	(66.7%)
length of time on GFD (months) – 0mo	Continuous	12		107.1
HLA-DQ status - DQ2 homozygous	Dichotomous	12	5	(41.7%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	12	5	(41.7%)
HLA-DQ status - DQ2/8	Dichotomous	12	1	(8.3%)
HLA-DQ status - not measured/unknown	Dichotomous	12	1	(8.3%)
Negative EMA at diagnosis	Dichotomous	12	10	(83.3%)
Dubious EMA at diagnosis	Dichotomous	12	2	(16.7%)
Negative tTGA at diagnosis	Dichotomous	12	11	(91.7%)
Dubious tTGA at diagnosis	Dichotomous	12	1	(8.3%)
primary RCD	Dichotomous	12	6	(50.0%)
secondary RCD	Dichotomous	12	6	(50.0%)
first-line treatment	Dichotomous	12	8	(66.7%)
second-line treatment	Dichotomous	12	4[a]	(33.3%)

a due to intolerance or resistance to azathioprine or corticosteroid dependency

Results

	Tioguanine		
	N	**k**	**mean**

Clinical response:					
body mass index (kg/m2) – 0mo (median)	Continuous	12		19.5 [rng 16.7–27.8]
body mass index (kg/m2) – 12mo (median)	Continuous	12		22.4 [rng 19.7–27.1]
body weight (kg) – 0mo (median)	Continuous	12		56.5 [rng 46–86]
body weight (kg) – 12mo (median)	Continuous	12		65 [rng 53–84]
proportion achieved – mo	Dichotomous	12	10	(83.3%)
Serological response:				
mean haemoglobin (mmol/L) – 0mo (median)	Continuous	12		7.7 [rng 6.5–9.7]
mean haemoglobin (mmol/L) – 12mo (median)	Continuous	12		8 [rng 7.3–9.9]
mean albumin level (g/L) – 0mo (median)	Continuous	12		38 [rng 27–44]
mean albumin level (g/L) – 12mo (median)	Continuous	12		40 [rng 32–45]
Histological response:				
proportion achieved improvement – 18mo	Dichotomous	9	7[a]	(77.8%)
no response – mo	Dichotomous	9	2[b]	(22.2%)
Marsh IIIC – 0mo	Dichotomous	12	1	(8.3%)
Marsh IIIC – 12mo	Dichotomous	9	0[c]	(0.0%)
Marsh IIIC – 24mo	Dichotomous	8	0[d]	(0.0%)
Marsh IIIB – 0mo	Dichotomous	12	2	(16.7%)
Marsh IIIB – 12mo	Dichotomous	9	1*c*	(11.1%)
Marsh IIIB – 24mo	Dichotomous	8	0*d*	(0.0%)
Marsh IIIA – 0mo	Dichotomous	12	9	(75.0%)
Marsh IIIA – 12mo	Dichotomous	9	2*c*	(22.2%)
Marsh IIIA – 24mo	Dichotomous	8	1*d*	(12.5%)
Marsh II – 0mo	Dichotomous	12	0	(0.0%)
Marsh II – 12mo	Dichotomous	9	1*c*	(11.1%)
Marsh II – 24mo	Dichotomous	8	0*d*	(0.0%)
Marsh 0 – 0mo	Dichotomous	12	0	(0.0%)

	Marsh 0 – 12mo	Dichotomous	9	5*c*	(55.6%)
	Marsh 0 – 24mo	Dichotomous	6	1[e]	(16.7%)
	Adverse events:				
	leukopenia	Dichotomous	12	0	(0.0%)
	liver test abnormalities – 3wk	Dichotomous	12	1[f]	(8.3%)
	muscle spasm – 9mo	Dichotomous	12	1[g]	(8.3%)
	anaemia	Dichotomous	12	0	(0.0%)
	thrombopaenia	Dichotomous	12	0	(0.0%)
	Survival/overall mortality:				
	overall mortality – 4mo	Dichotomous	12	1[h]	(8.3%)
	a achieved at average 18 months (one beyond 48m); not determined in 3 *b* after 12 to 14 months (these patients had clinical response) *c* not determined in 3 *d* not determined in 4 *e* not determined in 4; 4 of those who had achieved Marsh 0 at 12 months were not measured again at 24 months *f* gama glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase all 2x limit (alkaline phosphatase normal) not responding to dose reduction; withdrawn after 17 months due to achievement of clinical &histological response (values returned to normal during follow-up after cessation of tioguanine) *g* causing withdrawal from treatment (resolved after treatment stopped & corticosteroids started); no lab abnormalities; patient refractory to previous azathioprine treatment *h* progression of RCDI with severe diarrhoea not responding to prednisone, severe metabolic dysregulation including metabolic acidosis, hypokalaemia & hypoalbumaenia complicated with septic shock & multi-organ failure				
	Follow-up at average of 14 months ranging from 8 weeks to 8 years; study reports that four of the 10 patients who tolerated treatment for at least 6 months had been using corticosteroids at baseline (prednisone > or = 10 mg or budesonide > or = 9 mg) and 2 were dependent on corticosteroids during follow-up - all showed clinical response but only 2 showed histological response				

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

Bibliographic reference (Ref ID)	**Wahab,P.J. et al. (2000)**
Study characteristics	**Study design:** case series **Prospective/retrospective:** Prospective

	Consecutive patients: unclear **Country:** Netherlands
Patient characteristics	**Recruitment period:** between 1993 and 1997 **Inclusion criteria:** adults with refractory CD treated as out-patients **Definition of RCD:** malabsorption in the prescencce of gluten-related partial, subtotal or total villous atrophy on small intestinal biopsy supported by additional arguments for gluten-free sensitivity before starting a GFD (such as serum antigliandin and/or antiendomysial antibodies) **Exclusion criteria:** other possible pathology which could be responsible for malabsorpotion in the presence of villous atrophy such as: bacterial overgrowth, giardiasis, eosinophilic enteritis, hypgammaglobulinaemic sprue, lymphoma, carcinoma and collagenous colitis (determined from histological, serological and radiological investigations) **Length of time on a gluten-free diet:** at least 1 year **Description of gluten-free diet (and how adherence was monitored):** not reported; compliance determined from repeated interviews and dietary advice by the treatment team, including a dietician **RCD type:** not reported **Number of patients included:** 13 **Concomitant conditions:** a number excluded (see exclusion criteria); authors noted that no other concomitant conditions were noticed in these patients
Treatment	**Details:** treatment given for 2 months in all but then continued for up to a year in those who had histological improvement and/or symptom resolution **Arm No:** 1 **Name:** Cyclosporin **N:** 0 **Pharmacological agent:** cyclosporin agent 1: administration: oral agent 1: dosage (oral): 5 Comments: divided in 2 doses per day
Other	**Source of funding:** not reported **Authors' conflicts of interest:** not reported
Notes on outcomes	**Clinical response** – defined as patient symptoms after treatment improved (ie. improvement of fatigue, abdominal complaints and diarrhoea); those without response had no change in symptoms

	histological response – improvement considered a nomalisation of villi (to Marsh I or II)) **Notes: Cyclosporin serum concentration, range of antigliandin antibodies (IU/mL), and change in sugar absorption were reported in the study but not extracted.**

Baseline characteristics

		All study participants		
		N	**k**	**mean**
Patient characteristics:				
Age	Continuous	13		55[a]
Sex (n female)	Dichotomous	13	12	(92.3%)
length of time on GFD (months)	Continuous	13		86.8
HLA-DQ status - DQ2 homozygous	Dichotomous	13	5	(38.5%)
HLA-DQ status - DQ2 hetergozygous	Dichotomous	13	5	(38.5%)
HLA-DQ status - not measured/unknown	Dichotomous	13	3	(23.1%)
Negative EMA at diagnosis	Dichotomous	5	3[b]	(60.0%)
Dubious EMA at diagnosis	Dichotomous	5	2*b*	(40.0%)

a range 32-75
b 8 did not have the test done

Results

		Cyclosporin		
		N	**k**	**mean**
Clinical response:				
proportion achieved – 2mo	Dichotomous	13	8[a]	(61.5%)
proportion not achieved – 2mo	Dichotomous	13	5	(38.5%)
Histological response:				
proportion achieved improvement	Dichotomous	13	6	(46.2%)
Marsh IIIC – 0mo	Dichotomous	13	4	(30.8%)
Marsh IIIC – 2mo	Dichotomous	13	2	(15.4%)

	Marsh IIIC – 12mo	Dichotomous	7	0	(0.0%)
	Marsh IIIB – mo	Dichotomous	13	2	(15.4%)
	Marsh IIIB – 2mo	Dichotomous	13	0	(0.0%)
	Marsh IIIB – 12mo	Dichotomous	7	0	(0.0%)
	Marsh IIIA – mo	Dichotomous	13	8	(61.5%)
	Marsh IIIA – 2mo	Dichotomous	13	9	(69.2%)
	Marsh IIIA – 12mo	Dichotomous	7	3	(42.9%)
	Marsh II – mo	Dichotomous	13	0	(0.0%)
	Marsh II – 2mo	Dichotomous	13	3	(23.1%)
	Marsh II – 12mo	Dichotomous	7	4	(57.1%)
	Marsh I – mo	Dichotomous	13	0	(0.0%)
	Marsh I – 2mo	Dichotomous	13	1	(7.7%)
	Marsh I – 12mo	Dichotomous	7	0	(0.0%)
	Overall response:				
	Clinical and/or histological response	Dichotomous	13	7[b]	(53.8%)
	Adverse events:				
	nausea and abdominal cramps	Dichotomous	13	2	(15.4%)
	gingivitis	Dichotomous	13	1	(7.7%)
	a *6 also had improvement in histology* *b* *all patients continued treatment beyond 2 months*				
	All patients were treated for at least 2 months and 7 received treatment beyond this for up to a year (mean of 7.3 months, range 6 to 12)				

Abbreviations

CD – coeliac disease

CT – computerised tomography

DBE – double-balloon enteroscopy

EATL – enteropathy-associated T-cell lymphoma

EMA – anti-endomysial antibodies

EN – enteral nutrition

GI – gastro-intestinal
GFD – gluten-free diet
HLA-DQ2/ HLA-DQ8 – human leukocyte antigen serotypes
IEL – intraepithelial T-lymphocyte
IQR – intraquartile range
MRT – magnetic resonance tomography
PET – positron emission tomography
PCR – polymerase chain reaction
RCD – refractory coeliac disease
TCR – T-cell receptor
TPN – total parenteral nutrition
UJ – ulcerative jejunitis
VCE – video capsule endoscopy
WHO – World Health Organisation
2-CDA – cladribine

D.10 Review question 6.3

Bibliographic reference	No studies were identified for this question
Study type	
Study quality	
Number of patients	
Patient characteristics	
Intervention	
Comparison	
Length of follow up	
Location	

Bibliographic reference	No studies were identified for this question
Outcomes measures and effect size	
Source of funding	
Comments	*No studies were identified for this question*

(b) No studies identified

D.11 Review question 6.4

Bibliographic reference	Tack et al 2011 (REF ID: 65) Al-toma et al 2007 (REF ID: 251) Note: Tack (2011) study was an extension of the Al-toma (2007) study.
Study type	Case series
Study quality	Very low quality
Number of patients	Total number of eligible patients = 18
Patient characteristics	**Inclusion criteria** • Patients aged <70 years and diagnosed with RCD type II • Showed no response to one or two courses of cladribine for 5 consecutive days. • A lower percentage of aberrant T cells was allowed in the presence of ulcerative jejunitis. **Exclusion criteria** • Enteropathy-associated T-cell lymphoma (EATL) was excluded (based on the diagnosis according to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues). • Patients with severe concomitant cardiac, pulmonary, renal or hepatic disease. • Patients with active uncontrolled infection and HIV positivity. **Diagnosis of RCD type II**

<table>
<tr><th>Bibliographic reference</th><td>Tack et al 2011 (REF ID: 65)
Al-toma et al 2007 (REF ID: 251)
Note: Tack (2011) study was an extension of the Al-toma (2007) study.</td></tr>
<tr><td></td><td>

The diagnosis of RCD II was based on persisting or recurring symptoms and small intestinal villous atrophy after a former good response despite strict adherence to a gluten-free diet for at least 1 year.
Furthermore, the clinically validated cut-off value of 420% aberrant IEL detected by flow cytometric analysis was used to distinguish RCD type I and type II.

Patient characteristics
Total number of eligible patients = 18
The median time between cladribine treatment and auto-SCT = 6.25 months.

All patients entered the treatment protocol, however 5 patients did not make it to auto- SCT: i) unsuccessful leukapheresis = 2; ii) progression into EATL occurred before stem cells could be collected = 3

Median follow-up time for the 13 auto-SCT patients = 26 years (range: 10 to 67 months)
<table>
<tr><th></th><th>Transplanted (n=13)</th><th>Nottransplanted (n=5)</th></tr>
<tr><td>Gender: Female/Male</td><td>7:6</td><td>3:2</td></tr>
<tr><td>Age at CD diagnosis (years): Median (range)</td><td>50 (37–68)</td><td>63 (45–66)</td></tr>
<tr><td>Age at RCDII diagnosis (years): Median (range)</td><td>58 (42–68)</td><td>64 (47–70)</td></tr>
<tr><td>Age at (intention to) auto-SCT (years): Median (range)</td><td>59 (43–68)</td><td>65 (52–70)</td></tr>
<tr><td>Treatment before auto-SCT:
Cladribine
Azathioprine/Prednisone</td><td>
13
3</td><td>
5
2</td></tr>
<tr><td>Time between cladribine and auto-SCT (months): Median (range)</td><td>6.25 (3–30)</td><td></td></tr>
<tr><td>Follow-up time (months): Median (range)</td><td>26 (10–67)</td><td>5.5 (1–12.5)</td></tr>
</table>
</td></tr>
<tr><th>Intervention</th><td>Autologous hematopoietic stem cell transplant (Auto-SCT)</td></tr>
</table>

Bibliographic reference	**Tack et al 2011 (REF ID: 65)** **Al-toma et al 2007 (REF ID: 251)** **Note: Tack (2011) study was an extension of the Al-toma (2007) study.**
	• Mobilization of hematpoietic progenitor cells from the BM into the peripheral blood was achieved using G-CSF injection daily for at least 4 days without preceding chemotherapy. • The conditioning regimen consisted of fludarabine administered orally for 5 days (40 mg/m2 per day) and intermediate dose melphalan (administered i.v., 2 days, 70 mg/m2 per day) • At day 0 stem cells were reinfused. • All patients received standard antibacterial and antifungal prophylaxis during neutropenia and trimethoprim–sulfamethoxazole gluten free syrup 480–960 mg daily until 6 months after transplantation. • Total parenteral nutrition and blood and platelet transfusions were given if indicated.
Comparison	N/A
Length of follow up	Median in months (range) = 26 (10–67)
Location	Recruitment: between March 2004 and February 2010 Tertiary hospitals: Amsterdam = 15; Italy = 1; Germany = 1; Portugal = 1 (total 18 eligible) (locations for the 13 patients who went through Auto-SCT were not reported)
Outcomes measures and effect size	**Mortality:** Transplant group = 23% (3/13) Nottransplant group = 100% (5/5) [all died within a median follow-up of 5.5 months (range 1–12.5 months)]. (death due to EATL: Transplant group = 1; Nottransplant group = 4) **Overall survival after auto-SCT (unresponsiveness to cladribine therapy):** Transplant group: Overall 3-year survival = 80% Overall 4-year survival = 66% **Complete histological remission (defined as Marsh 0 or I):** Transplant group = 38% (5 of 13)

Bibliographic reference	**Tack et al 2011 (REF ID: 65)** **Al-toma et al 2007 (REF ID: 251)** **Note: Tack (2011) study was an extension of the Al-toma (2007) study.**
	Aberrant intestinal T lymphocytes: Transplant group (median percentage): Before = 45%; After = 54% All transplanted patients reached follow-up of almost 1 year to assess remission status. Within 1 year after auto-SCT, the majority of patients (11 of 13) showed impressive clinical improvement with normalization of stool frequency, disappearance of gastrointestinal symptoms and normal levels of or improvement of ≥1 point in BMI, albumin and/or Hb. **All patients had a WHO performance status of 0 at the end of follow-up:** Before ASCT: 7/13 (54%) After ASCT: 13/13 (100%)
Source of funding	This study was supported by an unrestricted grant from AstraZeneca.
Comments	Very small number of cases, no comparison to other treatment due to the narrow inclusion criteria (RCD type II, unresponsive to cladribine therapy), a proportion of the patients had EATL. Hence, the limited inconclusive evidence cannot be generalised to the overall RCD patients.

D.12 Review question 7.1

Bibliographic reference	**Nordyke (2011): Mass screening for celiac disease from the perspective pf newly diagnosed adolescents and their parents: A mixed method study**
Study type and aim	Nested case-referent study
Study quality	Was there a clear statement of the aims of the research? Yes – aim is clear Is a qualitative methodology appropriate? Yes – appropriate methodology for this type of research question Was the research design appropriate to address the aims of the research? Yes – design was appropriate Was the recruitment strategy appropriate to the aims of the research? Yes – all screening participants included Was the data collected in a way that addressed the research issue? Yes – standardised HRQOL Eq5D used

Bibliographic reference	Nordyke (2011): Mass screening for celiac disease from the perspective pf newly diagnosed adolescents and their parents: A mixed method study
	Has the relationship between researcher and participants been adequately considered? Not clear Have ethical issues been taken into consideration? Yes – study approved by ethical board Was the data analysis sufficiently rigorous? Yes – all EQ5D data analysed Is there a clear statement of findings? Yes How valuable is the research? Valuable
Number of patients	N=103 CD and 483 non-CD
location	Sweden
Patient characteristics	**Inclusion criteria:** 10041 children invited and 7567 consented to participate. 6th graders from 5 regions in Sweden when they were 12 years old. 145 had screening detected CD and 61 reported CD prior to screening. 4 refernts per CD child were randomly chosen to match age and gender **Exclusion criteria**: 2 participants with CD were found not to have CD (61 diagnosed prior and 144 screening-detected CD cases) **Mean age at diagnosis**: 13.4 **Mean age at follow-up:** 14.6
Intervention	Mass screening for CD
Investigations	Questionnaire: EQ5D Swedish child-friendly pilot version Baseline questionnaires were filled out before results fed back to participants Questionnaires mailed out to participants one year at follow-up Responses were included for the screening-detected cases and respondents when they answered all 5 dimensions Cases = 103 Referents = 483 VAS thermometer also filled out where fill in health today from worst to best imaginable (0 - 100)

Bibliographic reference	Nordyke (2011): Mass screening for celiac disease from the perspective pf newly diagnosed adolescents and their parents: A mixed method study
	Blood sample and biopsy Serological testing done. Biopsy confirmed CD. No further information on type of serological testing No further information on who was given biopsy (i.e. all seropositive?) or biopsy histological criteria for diagnosis
Length of follow up	1 year
Outcome	Change in EQ5D and VAS scores between cases and referents at baseline and at follow-up
Results	Eq5D and VAS Few participants reported severe symptoms, so collapsed into 'no problems' vs. 'problems'. HRQOL similar between cases and referents both at baseline and at follow-up Only dimension where difference was pain, where fewer cases reported problems than referents: OR = 0.50 (95% CI: 0.27 – 0.97) This only significantly different in boys at follow-up In anxiety dimension both cases and referents had small increase between baseline and follow-up (not significant) No significant change in VAS score between baseline and follow-up in either group
Source of funding	Study was supported by grants from the following: Swedish research council: Swedish research council for environment, agricultural sciences, and spatial planning; Swedish council for working life and social research grant, European union supported project
Comments	

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
Study type and aim	Qualitative cross-sectional study: uses interpretative phenomenological approach to enhance the understanding of how

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
	to support family adjustment to a GFD
Study quality	CASP QUALITATIVE TOOL: Was there a clear statement of the aims of the research? Yes - aim to understand impact on family of child with CD Is a qualitative methodology appropriate? Yes - no other method applicable Was the research design appropriate to address the aims of the research question? Yes - structured interview Was the recruitment strategy appropriate to the aims of the research? NO - unclear recruitment. No mention of how participants were found or approached Was the data collected in a way that addressed the research issue? Yes - thematic analyses of key interview themes undertaken Has the relationship between researcher and participants been adequately considered? NO - unclear relationship between researcher and participant, and who analysed data Has ethical issues been taken into consideration? Not applicable Was the data analysis sufficiently rigorous? Yes - key themes thoroughly explored Is there a clear statement of findings? Yes - thematic analyses and supportive quotes supplied in text How valuable is the research? Valuable - limited information available to date on impact on family of having a child with CD.
Number of patients	20 parents of 14 children interviewed
location	Sweden

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
Patient characteristics	**Inclusion criteria:** families of which children who had a definite diagnosis of CD and had been livin with the disease and a GFD for at least 2 years. Among those that met inclusion criteria consecutively chose 15 families with a child diagnosed with CD. All but one of the representatives consented to being interviewed. Interviewed in 3 groups: First group: parents whose children performed their first small intestine biopsy (SIB) before 2 years of age (7 children, 13 parents) at time of interview children between 3 and 5 years Second group parents whose children were >23 years when went through first SIB (3 parents and 3 children) Third group: parents whose children had performed first SIB before 2 years of age but were older than first group at time of interview (16 years old) Exclusion criteria: None listed **Mean age**: group 1: 4.3 years; group 2: 16.3 years, group 3: 16 years Mean age at diagnosis: NA Mean years since diagnosis: NA
Signs and symptoms	NA
Investigations	Interview: Interview took place in home Recorded all interviews and used semi-structured interview guide that includes open ended questions about how parents experienced their children's disease Depending on parents answers, asked follow-up questions to obtain a deeper understanding of their experiences

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
	Transcribed verbatim and exhaustively examined for references to similarities and differences Then identified sections of the text that illustrate how parents experience their children's disease before and after diagnosis and how manage to adopt a GFD Then chose among the examples to find those that most obviously captured participants' thoughts and beliefs
Length of follow up	
Outcome	Resolution of symptoms Patient experience Complications of cd Adherence Health related quality of life Impact on carers
Results	Organized results into 2 categories with subthemes: 1) struggle to understand child's disease before the diagnosis; 2) process of transforming to a GFD Struggle to understand disease Mother of a 5 year old boy suspected something was wrong with her son when she tried to give him ordinary food – " when we gave him ordinary food hejust cried…he bawled through meals" 5 year old lost weight dramatically – " she lost more than a kilo so she was really weak. It was terrible" One parent did not suspect. Her child was coincidentally tested with no symptoms – " she never showed any symptoms, she had never been sick"

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
	Parents described process of gaining understanding among HC professionals before the diagnosis as a ‘struggle’ and concerns not taken seriously Mother 4 year old, 5 months to diagnosis. Staff at well-baby clinic told her not to worry – “ I felt everything was not as it should be. They went against me many months before the diagnosis was made. Now looking back, I regret I did not stand my ground more than I did or go to a private doctor”. Most of parents said they were relieved when they knew what was wrong with their child Mother 4 year old girl – “it was wonderful to get the diagnosis. It was a relief” Getting diagnosis meant parents knew how they could help their child to reduce symptoms Transforming to a GFD Most parents reported rapid normalization process to a GFD. One mother of 2 year of said was confused for about 2 months after diagnosis – “I panicked about everything…the first 2 months were a mess. Parents express appreciation of child’s response to GFD – “as she gets older she is more aware of this” Mother 17 year old who got diagnosis as teen said harder for her child – “it might be different if she got sick as soon as she ate gluten food. Theyn you know you cannot eat this because you will get sick and not feel well afterwards” Parents whose children were diagnosed when young have had opportunity to socialize their children into a GFD. These children usually haven’t experienced taste of gluten food and were not aware of what they are missing. Mother of 5 year old could not stop worrying about what woud happen if her daughter tasted something she should not eat – 2 it is always ther that she could get access to crumbs”

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
	Most parents reported seldom visited restaurants for reason such as not trusting staff's description of ingredients or lack fo food for child One parent spoke of restricted leaisure activities for her 16 year old son – " he cannot spontaneously be with his oeers, everything has to be checked and questioned if he eats with them, I think he fears his peers will think he is a bother to be with. I think the disease hinders him socially" Parents said travelling could be demanding because of difficulties getting acces to propoer food Visiting houses can be difficult. One parent always called house before to check food and make soue would be GF food available Expressed struggle to get staff at daycare and school to understand their childrens GFD Daycare staff not sufficiently educated Negative attitudes from staff at school's dining hall Parents actively and constantly try to find out as much as possible about the disease and how to meet childs GFD needs. Aprents of a 3 year olf search for knowledge through people who know about the disease, on the internet, and through the CD association Most parents have regular contact with a dietician Parents have concerns for children's future. Mother of 5 year olf worries about how child will cope when living alone Parents put hope into new treatments based on scientific breakthroughs
Source of funding	Swedish society for coeliacs, FORSS and the Swedish research council

Bibliographic reference	Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
Comments	

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
Study type and aim	Mixed-method using both qualitative and quantitative study designs, which aimed to explore adolescent' and parent' experiences having the adolescent' CD detected through mass screening and their attitudes towards possible future screening
Study quality	Was there a clear statement of the aims of the research? Yes – aim is clear Is a qualitative methodology appropriate? Yes – appropriate methodology for this type of research question Was the research design appropriate to address the aims of the research? Yes – design was appropriate Was the recruitment strategy appropriate to the aims of the research? Yes – all screening participants included Was the data collected in a way that addressed the research issue? Yes – standardised focus groups structured and questionnaires were validated in previous study Has the relationship between researcher and participants been adequately considered? Not clear Have ethical issues been taken into consideration? Yes – study approved by ethical board Was the data analysis sufficiently rigorous? Yes – all data sufficiently rigorously analysed Is there a clear statement of findings? Yes How valuable is the research? Valuable
Number of patients	N=145

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
location	Sweden
Patient characteristics	**Inclusion criteria:** Same pool of participants described in Nordyke (2013). All 145 screening-detected and biopsy-verified CD cases and their parents were contacted for this study. 31 adolescents and 43 parents participated in focus group discussions, 91 adolescents and 105 parents submitted written narrative, and 114 parents filled in questionnaires **Exclusion criteria**: **Mean age of adolescents:** 14.6 years **Mean age since diagnosis:** 15.9 months
Intervention	N/A
Investigations	Focus group discussion: Families in four of the five study sites invited to participate 14 focus groups held involving 31 adolescents and 43 parents Main reason non-participation was lack of time, but a few adolescents expressed reluctance to discuss their disease – parents of the latter did participate Adolescents and parents attended different groups Flexible topic guide and hypothetical case stories used to stimulate discussions and infomants encouraged to discuss issues most important to them Topic guide focussed around informants reasoning when deciding to take part in a screening, and their attitudes towards CD mass screening All interviews digitally recorded Recordings transcribed and later cross-checked to ensure accuracy Transcribed texts entered into Open code Follow-up questionnaires Short reflective narratives Adolescents and their parents asked to write narratives Encouraged to reflect on their overall experience of CD screening and specifically to elaborate on both how they felt about receiving diagnosis and on their recommendation about possible future CD screening Length = one or two hand written pages

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
	All narratives entered into Open Code software Questions on future screening Parental questionnaire included 2 questions that were utilised in this study: I) whether a CD screening should be implemented (Y/N) At what age screening should be conducted (open answer)
Length of follow up	1 year post diagnosis
Outcome	Adolescents and parents' reported experiences of process of CD diagnosis and consequences of this
Results	**Immediate Reaction to the diagnosis:** '**like a bolt of lightning' – changed life**: adolescents – 75% parents 70% emphasized that more specific information about the consequences of the screening]and having CD] should be given before the test researhers informed parents over the phone and parents were messengers to their children adolescents described this as awkward because neither they nor their parents knew what it really meant this lack of knowledge fostered anxiety among both parents and adolescents "[when receiving the results] I wasn't totally sure either, but I had a little hop[e that maybe it wasn't so, but what was it then? Something even worse… I was scared about that and searched the internet and got nightmares that it was something even worse" –mother Some adolescents felt betrayed by the information given before the test, as they thought it had not sufficiently prepared them for the consequences of participating in the screening. Described being disappointed by their parents having decided on their behalf for them to participate worlds like "getting caught" or getting stuck frequently used to describe receiving the diagnosis **Suddenly everything made sense – adolescents 5% parents 18%** Some described how the diagnosis came as a relief as they had had unexplained symptoms "We'd been to paediatric clinics earlier for different diffuse problems, so when we found out about this, it was as if it suddenly dawned on me" – father

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
	<u>Looking back at screening</u> **Feeling grateful for being made aware – 38% adolescents, 72% parents** Knowledge of previously undetected diagnosis was perceived as important and both expressed gratitude Reasons differed depending on adolescents perceived health before the screening If had symptoms becoming aware of diagnosis gave them a means to feel better Adolescents who had no symptoms expressed screening even more important to them as they would not have known about the disease “You’re happy when it’s detected. Since she wasn’t sick, its even better that we found out now. It could have gone on forever.” Both concerned about future complications – these different based on which centre diagnosed at Some sites greatest concern was developing diabetes, others it was cancer risk “ I think knowing is positive. I think It would be worse not knowing and risk of developing all those complications” – father “I think you’re more motivated to eat gluten-free food than to not start smoking because smoking is still your own choice” girl “If you get the recommendation to eat gluten-free food, then it’s more personal.” Boy “it sort of feels more important” girl **Ambivalent feelings towards personal benefit 10% adolescents, 8% parents** Some were ambivalent – this was associated with not perceiving any health improvement and being ambivalent about whether heath complications would really occur This also related to social consequences of having to adhere “I got very annoyed when the doctor called and said that I was gluten intolerant, not because I was gluten-intolerant, but because I had no symptoms.”
Source of funding	
Comments	
Bibliographic reference	**Hogberg (2003): Better dietary compliance in patients with coeliac disease diagnosed in early childhood**

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
Study type and aim	Cross sectional study to assess whether young adults diagnosed with CD before the age of 4 have better dietary compliance than those diagnosed later in life
Study quality	Was there a clear statement of the aims of the research? Yes – aim is clear Is a qualitative methodology appropriate? Yes – appropriate methodology for this type of research question Was the research design appropriate to address the aims of the research? Yes – design was appropriate Was the recruitment strategy appropriate to the aims of the research? Yes – all screening participants included Was the data collected in a way that addressed the research issue? Yes – standardised protocol for serological testing used. Specifics of questionnaire used not listed Has the relationship between researcher and participants been adequately considered? Not clear Have ethical issues been taken into consideration? Yes – study approved by ethical board Was the data analysis sufficiently rigorous? Yes – serological and questionnaire data analysed sufficiently Is there a clear statement of findings? Yes How valuable is the research? Valuable
Number of patients	29 adults with CD diagnosed at childhood
location	Sweden
Patient characteristics	**Inclusion criteria:** consecutively recruited for the study. Patients were consecutively diagnosed before 18 years of age in one clinic between 1975 and 1981. 9 men and 20 women. Group 1: n=15, aged 4 or younger at diagnosis. Group 2: n= 14, older than 4 years at diagnosis Diagnosis confirmed by biopsy in all according to ESPGHAN criteria. **Exclusion criteria**: noen listed **Mean age at diagnosis**: 5.8 (1.6 – 15.1) **Mean age at follow-up:** 26 (19 – 34)
Intervention	NA
Investigations	Questionnaire Sent by mail to participants

Bibliographic reference	Rosen (2011): Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed method study
	Sked how after had gluten in diet: never, once a year, once a month, once a week, or always Gluten intake > once a month considered non-compliance
Length of follow up	N/A
Outcome	Self-reported compliance and serological maker of compliance
Results	Questionnaire Dietary compliance significantly differed between the 2 groups from questionnaire measure Serology** 11/29 had elevated EMA 10/28 elevated TGA 80% patients in group 1 vs 46% in group 2 kept a GFD according to serology
Source of funding	Odd Fellow foundation, Sweden
Comments	
** Sera were collected 3 years before questionnaire was filled out!!	

Bibliographic reference	Kurppa (2014): Benefits of Gluten-free diet for asymptomatic patients with Serologic markers of Coeliac disease
Study type and aim	Study investigated whether screen-detected and apparently asymptomatic adults with positive EMA benefit from a glutenfree diet
Study quality	Was there a clear statement of the aims of the research? YES Is a qualitative methodology appropriate? YES Was the research design appropriate to address the aims of the research? NO: Particpants are EMA positive only, so there

Bibliographic reference	Kurppa (2014): Benefits of Gluten-free diet for asymptomatic patients with Serologic markers of Coeliac disease
	is no way to verify how many of this population actually have CD. Optimal research design would have confirmed CD diagnosis histologically. Was the recruitment strategy appropriate to the aims of the research? YES Was the data collected in a way that addressed the research issue? YES Has the relationship between researcher and participants been adequately considered? UNSURE Have ethical issues been taken into consideration? MAYBE; EMA positive individuals were randomised to either GFD or Gluten containing diet for one year. It is possible that the QoL of those with positive EMA who were randomised to gluten containing diet would have significantly benefited from a GFD and their diagnosis of CD was delayed by at least a year. However, if patients exhibited significant symptoms they were withdrawn from the study for further investigation. The authors justify their methodology with the statement that if they had not been part of this study these individuals would never had had testing for EMA anyway and therefore would have continued on their normal gluten containing diet Was the data analysis sufficiently rigorous? YES Is there a clear statement of findings? YES How valuable is the research? Highly valuable - no other studies exist which address this issue. Overall risk of bias = Low
Number of patients	40
location	Finland
Patient characteristics	**Inclusion criteria:** Positive EMA antibodies; aged between 18 - 75; absence of clinical symptoms; **Exclusion criteria**: <18 or >75; symptomatic of CD; Any concommittent conditions; pregnancy; **Mean age at diagnosis**:NA **Mean age at follow-up:** NA
Investigations	3031 individuals who were relatives of coeliac patients (deemed higher risk than the general population) screened for EMA. Of these, 108 were positive and of those, 40 met inclusion criteria. The following investigations were carried out: Serology and HLA genetics Gastrointestinal and heat-related quality of life - GSRS and VAS Laboratory parameters: haemoglobin; iron, folate, albumin

Bibliographic reference	Kurppa (2014): Benefits of Gluten-free diet for asymptomatic patients with Serologic markers of Coeliac disease
	Bone mineral density using X-ray Gastrointestinal endoscopy Questioned on dietary adherence and willingness to continue diet in the future
Length of follow up	2 year
Outcome	GSRS; VAS
Results	All study groups comparable in age sex medical history and associated medical conditions All subjects had HLA DQ2 or DQ8 status Baseline score GSRS = 1.8 (0.6) in GFD and 1.7 (0.6) in gluten group After intervention total GSRS significantly reduced in GFD group (p=0.49) Anxiety alleviated in GFD group in PGWB score (p=0.25) Mean change in SF-36 not significantly different between groups in any dimension Perception of current health as evaluated by VAS improved in the GFD group (p=0.17)
Source of funding	None listed
Comments	
Serological histological and bone mineral density not reported on here as not listed as relevant outcomes in the review protocol.	

D.13 Review question 7.2

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
– Study type and aim	– RCT to evaluate effect of psychosocial counselling on GFD compliance in CD patients
– Study quality	– **NICE RCT quality checklist:** – 15. Was an appropriate randomisation method used? No – method unclear

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	16. Was there adequate concealment of allocation? No – unclear 17. Were groups comparable at baseline? Yes – groups matched for age gender and education 18. Did the comparison groups receive the same care apart from the intervention of interest? Yes 19. Were participants receiving care kept blind to their treatment allocation? Not applicable 20. Were individuals administering care kept blind to treatment allocation? Not applicable 21. Were all groups followed for equal amount of time? Yes 22. Were groups comparable for treatment completion? Yes 23. Were groups comparable with respect to availability of outcome data? Yes 24. Did the study have an appropriate length of follow-up? Yes 25. Did the study use a precise definition of outcome? Yes, 26. Did the study use a valid and reliable method to determine outcome? Yes, standardised STAI measure used 27. Were investigators kept blind to participants exposure to intervention? Not applicable 28. Were investigators kept blind to other confounding and prognostic factors? Not applicable – – Unclear whether patients were consecutively recruited or how structured counselling sessions were and whether a single facilitator held these,however the patient flow, matching of groups in terms of intervention time and frequency and patient age, gender, and marital status were all clear. CD was biopsy confirmed for all patients and well-standardised psychometric tests were used to assess anxiety and depression. –
– Number of patients	– N=66
– location	– Italy
– Patient characteristics	– **Inclusion criteria:** out of all patients referred to outpatient centre between 1995 and 2003, 112 newly diagnosed adults with CD were considered. Out of these, 66 patients with anxiety and depression were considered for the study. Diagnosis based on positive antibodies and histological evidence of subtotal or total duodenal villous atrophy. Patients randomised into 2 groups selected as to match probands on the basis of gender, age, residence, employment, socio-economic, and marital status – **Exclusion criteria**: presence of psychiatric disorders other than anxiety and/or depression, endocrine disorders,

– Bibliographic reference	– Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders
	abuse of alcohol and/or other substances, consumption of psychoactive drugs, and/or current psychiatric treatment, and second causes of villous atrophy. – **Mean age**: Group A: 31.6; Group B: 29.8 – **Mean age at diagnosis**: – **Mean years since diagnosis**: –
– Intervention	– **Psychological support counselling** • Each subject of both groups was checked as an out-patient every 2 weeks for duration of the study • Group A: o Counselling performed as individual talks directed mainly to the stress management and, in particular, aimed at the identifying the cause and effect problems related to CD and at problems that the individual found difficult to resolve in the daily life and related to the |GFD. Counselling directed to evaluate and discuss dietary restrictions and related problems that lead to difficulty in social relationships. o Recognized that social occasions revolve around food and restrictions on eating can lead to decreased social life and onset of inadequacy and isolation. These feelings were evaluated at each session and counselling was directed at its regression. o During part of these meetings the family members living with the patient actively participated. • Group B: o Same time as was spent in counselling sessions was spent for the medical examination and clinical data evaluation. –
– Investigations	– Patients studied before and after 6 months on GFD. Blood sample collected every 2 months to determine AGA and EMA antibodies. – After 6 months, histological improvement or recovery assessed – Adherence to GFD assessed on basis of participant's self-reported and family member interview, by clinical symptoms and histological recovery, and by antibody results. – **Psychological assessment:** All patients given 2 self-rating psychometric tests: state-trait anxiety inventory (STAI), and self-rating depression scale (SDS) • STAI: 20 multiple choice; each otem has score 1-4 so that total can range from 20-80. Allows measurement of current

– Bibliographic reference	– Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders
	anxiety (Y1) as well as stable proneness to anxiety (Y2). Only Y1 was used here as previous study showed little difference between patients and controls in Y2. Subjects divided into high and low based on median value of 40. • SDS: Zung SDS modified to Ciacci 1998 version used. Original version contains 20 multiple choice score 1-4 each, total between 20 – 80 possible. Modified version does not contain 3 items relating to gastrointestinal symptoms of depression; a rough point score of 37 was considered high. • – The SDS and STAI were administered before and 6 months after GFD
– Length of follow up	– 6 months
– Outcome	• Resolution of symptoms • Patient experience • Complications of cd • <u>Adherence</u> • <u>Health related quality of life:</u> • Impact on carers
– Results	– **Health related quality of life:** • Anxiety: o Group A: At the end of the study 5/33 patients in Group A reported anxiety o Group B: At the end of the study 8/33 patients in Group B reported anxiety o No significant difference between the groups : Chi 2 = 0.58 • Depression: At the end f the study 5/33 patients in Group A reported anxiety o At the end of the study 5/33 patients in Group A reported depression o At the end of the study 26/33 patients in Group B reported depression o Significant difference between the groups: Chi 2 = 10.16 (15.1% vs 79%) – **Adherence:** • Group A : 3/33 showed poor compliance • Group B: 13/33 showed poor compliance • Significant difference: Chi 2 = 5.11 (39% vs 9%)

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	–
– Source of funding	– Supported by grants from Associazone Ricerca in Medicina' Bologna, Italy
– Comments	
– –	
– **Bibliographic reference**	– **Erichiello (2010): Celiac disease: predictors of compliance with a gluten-free diet in adolescents and young adults**
– Study type and aim	– Cross-sectional study to identify risk as well as protective factors related to compliance with the GFD in a cohort of teenagers with CD
– Study quality	**CASP QUALITATIVE TOOL:** 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research question? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Not applicable 7. Has ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? Valuable

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	–
– Number of patients	– N=204
– location	– Italy
– Patient characteristics	– **Inclusion criteria:** patients consecutively recruited from Campania region on basis of age between 13 – 30 years, CD diagnosis according to ESPGHAN, and willingness to participate. Patients were divided into 2 groups on basis of diagnosis before 13 years (group 1) and diagnosis after 13yrs (group 2) – **Exclusion criteria**: None listed – **Mean age**: 62% 13 – 19 years; 31% 19 – 26; 6.5% 26 – 30 years – **Mean age at diagnosis**: 86% diagnosis <13 years; 15% age at diagnosis > 13 years
– Signs and symptoms	• Abdominal pain – 10% • Constipation – 5% • Diarrhoea – 4% • Failure to thrive – 3.5% • Headache/neurological disturbance – 4.4% • Skin disease - 3% • No symptoms – 69.6%
– Investigations	• Each patient underwent complete clinical check-up • N=199 underwent antibody testing for TTG with immunosorbent assay – – **Standardized self-admin questionnaire** • Standardized self-admin questionnaire modified by previous study was used/ Psych working in the team adapted the form from internationally validated references ○ This was admin after a 2 day training session of the investigators ○ Evaluated family and social integration, integration within school environment, sexual life, on visual analogue sales rated 0 – 25 ranging from poor to excellent ○ Social integration investigated through description of the daily life of patients including: ▪ Number of outings

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	▪ Participation in social events, ▪ Number of friends ▪ Play activities o Feeling of self-constraint related to the GFD was also investigated o Smoking habit o School performance – – **Food habit assessment** • Managed by 2 dieticians • Patients questioned about their diet in the previous day, using standardised 1-day recall form, and about total amount of gluten-containing items available to this range of population • Daily gluten intake was estimated summing total amount of gluten containing foods ingested in previous 30 days
– Length of follow up	– N/a
– Outcome	• Resolution of symptoms • **Patient experience** • Complications of cd • Adherence • Health related quality of life • Impact on carers
– Results	– **Patient experience** • Self-rated social integration: 181 patients reported good family integration • 186 reported good social relationships • 180 reported good school integrations • 110 (54%) felt that CD occasionally or often limited their social life • Those with excellent school integration adhered to diet better than those with bad ofr sufficient integration – 83%. 50% of poor integration did not adhere to diet. • Good social relationships significantly related to compliance – 81%

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	• People without feelings of self-constraint adhered better than those without feelings of self-constraint – – **Adherence** • 97% of compliers tested TTG negative, 3% had positive titre despite compliance • 70% poor compliers had negative TTG, only 30% showed positive TTG • 111/150 good compliers had no health complaints • 31/54 poor compliers had no health complaints • Health complaints more frequent in compliers vs noncompliant
– Source of funding	– This work was supported by European laboratory for the investigation of Food-Induced Diseases and Italian Ministry of Instruction, University, and Research
– Comments	
– –	
– **Bibliographic reference**	– **Sainsbury (2013): A randomised controlled trial of an online intervention to improve gluten-free diet adherence in celiac disease**
– Study type and aim	– RCT (waitlist control) to test effectiveness of an interactive online intervention to improve GFD adherence in adults with CD
– Study quality	1. Was an appropriate randomisation method used? Yes – random email allocation 2. Was there adequate concealment of allocation? Yes – allocated via computer generation to private email 3. Were groups comparable at baseline? Yes – groups matched for all variables 4. Did the comparison groups receive the same care apart from the intervention of interest? Not applicable 5. Were participants receiving care kept blind to their treatment allocation? Not applicable 6. Were individuals administering care kept blind to treatment allocation? Not applicable 7. Were all groups followed for equal amount of time? Yes 8. Were groups comparable for treatment completion? Yes 9. Were groups comparable with respect to availability of outcome data? Yes 10. Did the study have an appropriate length of follow-up? Yes

– **Bibliographic reference**	– **Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders**
	11. Did the study use a precise definition of outcome? Yes, 12. Did the study use a valid and reliable method to determine outcome? Yes 13. Were investigators kept blind to participants exposure to intervention? Not applicable 14. Were investigators kept blind to other confounding and prognostic factors? Not applicable – **Overall risk of bias: serious:** Selection of patients, patient population, reference and index tests all match review criteria. However,patient flow is of concern as a number of participants are unaccounted for.
– Number of patients	– N = 189 (88 randomised to waitlist; 101 randomised to intervention)
– location	– Australia
– Patient characteristics	– **Inclusion criteria:** Participants recruited from coeliac society of NSW. Database screened to ID members who: had biopsy-confirmed CD; GFD of > 3 months; aged >16 years. Decision to include participants with varying levels of adherence at baseline to avoid excluding large number of participants who could still benefit even though report strict adherence as may be inadvertently be ingesting gluten – **Exclusion criteria**: none listed – **Mean age**: 46.5 years – **Mean age at diagnosis**: – **Mean years since diagnosis**: 4.6 years –
– Intervention	– Email sent to 1500 people who met inclusion criteria which linked to study site and baseline questionnaire. Study was outlined as program to help better manage challenges of GFD. – • Intervention admin online via LimeSurvey • Baseline Q's took 20 mins • 4 days later, randomized to: o Intervention condition – received an email link to study website to complete module 1 o Waitlist control – received an email informing them they would be contacted in 8 weeks to complete post-survey and would be given access to intervention materials at that time.

– Bibliographic reference	– Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders
	• Progression through 6 modules managed using automated emails and text messages • Had to complete module 1 to progress however was the possible to skip a module and remain active in the intervention – • Modules: o 1 – Education: about CD and GFD o 2 – Structured problem solving: to manage internal and external problems associated with GFD o 3 – Communication: styles of communication typical situation where asseritvess may be needed, steps to assertiveness; communicating about the GFD in order to receive safe meal while not drawing attention to self o 4 – thinking about GFD: rel between thoughts feelings anf behaviour – reactions to CD diagnosis and cognitive restructuring of negative thoughts o 5 – balancing life with GFD: effects of narrowed focus, pleasant activity scheduling, SMART goal-setting o 6 – Bringing it all together: summary of skills learned; label reading/avoiding contamination • Each module took 30mins to complete, one a week. • All participants in both groups sent post-survey questionnaire after specified period of time
– Investigations	– Measures: • At baseline, participants competed measures of demographic and CD info • Following questionnaire battery completed at baseline, post-intervention, and 3 month follow-up. – • GFD adherence measured using Celiac dietary adherence test (Leffler et al., 09)scores range 7 – 35, with higher score rep poorer adherence • Scores grouped into: o Excellent to fairly good (7 – 12) o Moderate (13- 17) o Fair to poor (18 – 35) • WHO QOL assessment BREF used to measure overall QoL and physical and psychological QoL • Psych symptoms assessed using depression, anxiety, stress scale and eating disorders inventory -3 eating disorder risk scale

– Bibliographic reference	– Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders
	• Knowledge assessed using lists adapted from educational materials used by the Celiac society
– Length of follow up	– 3 months
– Outcome	• Resolution of symptoms • Patient experience • Complications of cd • **Adherence** • **Health related quality of life** • Impact on carers
– Results	– **Baseline differences between groups** – Two groups did not differ at baseline on any of the demographic, adherence, QoL, or psych variables – – **GFD adherence** • Significant improvement over time in adherence for both conditions (F=8.89, p = 0.0002) • Time x condition interaction effect also significant (F=5.67, p=0.014) • Apored smaple t test intervention group improved adherence scores from baseline to poast (t=3.83) while waitlist control unchanged (t-0.42) • Intention to treat sample this represented a small to medium effect size (Cohens d = 0.69; interaction effect F = 6.49) – – **Clinical significance** • 43% waitlist inadequate adherence at baseline • Post test measure available 29/38 of these - 55% still classed as poor adherence 38% had improved their category • 39% intervention group had inadequate intercention at baseline • Of 26/39 participants for whom post data available for, 65% had improved adherence category , while 35% remained inadequate – – **3 month follow up** • Difference in GFD adherence from baseline to 3 month was still significant (t=3.63)

– Bibliographic reference	– Addolorato (2004): Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders
	• No difference between immediate post intervention and 3 months scores (t = 0.53) • Difference in knowledge from baseline to 3 month significant (t=4.39) • No diff from post-test to 3 month in knowledge (t=0.5) –
– Source of funding	– None
– Comments	
– –	

– Bibliographic reference	– Rashid (2005): Celiac disease: Evaluation of the diagnosis and dietary compliance in Canadian children
– Study type and aim	– Cross sectional study to characterise clinical features at presentation as well as associated disorders, family history, and evaluation of compliance with a gluten-free diet in children with CD
– Study quality	1. Could the selection of patients have introduced bias? NO – all patients who met inclusion criteria were included 2. Is there concern that the included patients do not match the review question? NO. all patients had biopsy confirmed CD 3. Could the conduct or interpretation of the index test have introduced bias? YES – data is about children, however data was given retrospectively by their parents. Inherent level of bias in terms of recall and perspective 4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO 5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO - 6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – all patients had biopsy confirmed CD diagnosis 7. Could the patient flow have introduced bias? NO – all patients had – **Overall risk of bias: low - Patient parents filled out forms on their behalf, however this was deemed to have a**

– **Bibliographic reference**	– **Rashid (2005): Celiac disease: Evaluation of the diagnosis and dietary compliance in Canadian children**
	low impact overall on the bias of the study
– Number of patients	– N= 168 children < 16 yrs old
– location	– Canada
– Patient characteristics	– **Inclusion criteria:** Survey was sent to all (n=5240) members of the Canadian celiac association. 3408 responded, and of these, 194 were children under 16 years/ 168/194 had biopsy-confirmed CD and were included in the study, – **Exclusion criteria**: respondents >16 years of age or without biopsy confirmation of diagnosis – **Mean age**: 9 yeas (2-15) – **Mean age at diagnosis**: 5 years (1-15)
– Signs and symptoms	– Abdominal pain and gas – 90% – Weight loss – 71% – Poor growth – 70% – Diarrhoea – 65% – Nausea and vomiting – 53% – Anaemia - 40%
– Investigations	– **Questionnaire** • Developed by canadian celiac association in collaboration with dept of epidemiology and medicine University of Ottowa. • 76 questions on demographics, clinical symptoms prior to diagnosis, associated disorders, family history • Series of celiac-specific questions about well-being and lifestyle • Members of CCA professional advisory board and 2 international experts on CD reviewed content of survey • Parents completing questionnaire on behalf of child asked to involve child in answering questions as much as possible –
– Length of follow up	– N/A
– Outcome	• **Resolution of symptoms** • **Patient experience** • Complications of cd

– **Bibliographic reference**	– **Rashid (2005): Celiac disease: Evaluation of the diagnosis and dietary compliance in Canadian children**
	• Adherence • **<u>Health related quality of life</u>** • Impact on carers
– Results	– **Adherence** • 95% strict adherers • 4% felt could be healthy without gluten in diet (“% all the time / 2% most of time) – **Resolution of symptoms** • After starting diet, 89% noted a significant improvement in health • Accidental consumption triggered reaction in 54% of children – **Patient experience / health related QoL** • 13% felt left out of activities at school or friends’ homes • 18% felt different from other kids at school because of CD • 23% felt embarrassed to bring GF food to birthday parties • 23% felt angry about having to follow a special diet • 11% felt that their teachers and friends did not understand • 52% avoided restaurant • 15% avoided travelling • 28% found it difficult to buy GF foods at stores • 27% found ti difficult to determine if food was GF from label • 10% felt they were not invited out for meals because of CD • 13% worried about staying in hospital because of CD
– Source of funding	–
– Comments	
– –	

8b

– **Bibliographic reference**	– **Olsson (2008): The everyday life of adolescent coeliacs: issues of the importance for compliance with the gluten-free diet**
– Study type and aim	– Qualitative cohort study to assess how adolescents with CD perceive and manage their everyday lives in relation to a GFD
– Study quality	**CASP QUALITATIVE TOOL:** 1. Was there a clear statement of the aims of the research? YES 2. Is a qualitative methodology appropriate? YES 3. Was the research design appropriate to address the aims of the research question? YES 4. Was the recruitment strategy appropriate to the aims of the research? YES 5. Was the data collected in a way that addressed the research issue? YES 6. Has the relationship between researcher and participants been adequately considered? YES 7. Has ethical issues been taken into consideration? YES 8. Was the data analysis sufficiently rigorous? YES 9. Is there a clear statement of findings? YES 10. How valuable is the research? Valuable – thorough and well planned analyses and report of patient reported outcome relating to adherence to a GFD and the difficulties associated with this – **Overall risk of bias:**
– Number of patients	– N = 47

– **Bibliographic reference**	– **Olsson (2008): The everyday life of adolescent coeliacs: issues of the importance for compliance with the gluten-free diet**
– location	– Sweden
– Patient characteristics	– **Inclusion criteria:** confirmed CD based on ESPGHAN criteria. Age range 15 – 18, a prescription of GFD for at least 1 year. A prospective incidence register, which has nationwide coverage since 1998 and local paediatric depts. were used to ID potential participants. From these databases, 159 adolescents fulfilled the inclusion criteria, and were invited by letter with info about the study. 47 were recruited and interviewed. For each focus group, 6 to 7 adolescents were invited and 3- 6 participated. The first recruitment generated 6 focus groups. A second recruitment was conducted which generated 4 additional groups. – **Exclusion criteria**: None listed – **Mean age**: 16 – **Mean age at diagnosis**: 0 – 4 years – **Mean years since diagnosis**: 15 –
– Signs and symptoms	–
– Investigations	– **Focus group interviews**: • Adolescents spoke about beliefs, perceptions, expectations, needs, and experiences in relation to CD and the GFD • Interviews focused on social life, how they perceived different situations and obstacles • In all interviews first author was moderator and one of other authors acted as assistant. • Interview lasted 60 – 80mins and were digitally recorded • For all interviews, interview shaped by topic guide consisting of illustrative statement and open-ended questions • These consisted of experiences related to eating and being on a GFD in different contexts; everyday life in terms of knowledge, attitudes, support, and reactions in other people, and views of self in relation to CD. • Core topics same in each session • To establish credibility, participants were encourages to share their experiences, and the moderator went back over the conversations to verify findings. – Analysis of interview data • Focused on problems describes as most central and how they tried to sole these by different strategies • First author complied notes immediately after interview and described the recorded discussions verbatim • Transcripts read repeatedly by all authors and thereafter analysed in 3 stages according toStraus & Corbin (1998)

– **Bibliographic reference**	– **Olsson (2008): The everyday life of adolescent coeliacs: issues of the importance for compliance with the gluten-free diet**
	methods • Open coding first used to obtain overview of the info and conceptualize data • During this process new codes emerged and some codes were renamed or modified when going back and forth in the transcripts • Most important codes compared in order to find similarities between them and group into categories • Text segments from interviews then categorized using MAXqda2 software • After categorising patterns and themes emerged • For validity all authors were involved in data analysis
– Length of follow up	– n/a
– Outcome	• Resolution of symptoms • **Patient experience** • Complications of cd • Adherence • **Health related quality of life** • Impact on carers
– Results	– **Patient experience/ health related quality of life** – – GFD in everyday life • Most raised easier compliance at home compared with other places • Socially convenient circumstances at home where do not need to ask questions or explain diet • Situations outside home troublesome due to limited support and lack of disease-related knowledge in significant others (teachers, school kitchen staff, friends, grandparents) • Dissatisfaction with availability and sensory quality of GF foods • Attitudes and behaviours of signif. Others affected decision to comply or not in social situations • Limited knowledge about CD/GFD impaired social support and reinforced feelings of social inconvenience • Felt embarrassed when served special meals at school, socially inconvenient

– **Bibliographic reference**	– **Olsson (2008): The everyday life of adolescent coeliacs: issues of the importance for compliance with the gluten-free diet**
	• Being served same food as everyone i.e. at home or CD camps was very socially convenient – Different approaches to GFD: – Compliers who strictly follow, occasional noncompliers mostly eating GFD and resorting to GD in problematic situations; noncompliers, principally eating normal diet. • Compliers: ○ Presence of obvious signs and symptoms after gluten ingestion important motivator for adhering ○ Appropriate knowledge about importance of following strict GFD also contributed to compliance ○ Compliers saw options for finding acceptable solutions in different situations outside of home and usually found something to eat and if GF food not available still abstained from choosing gluten-containing food. ○ Also took control by planning and foresight by either bringing own food when were i.e. travelling or at sports camps ○ Consensus that normal food tasted better, but best strategy to manage this was to never expose self to sensory aspects of normal food ○ Practical and/or emotional support from significant others facilitated compliance i.e. by helping with bread baking, routinely offering GF alternatives, or just recognizing the importance of following a strict GFD were good enough motivators for compliance • Occasional compliers ○ Whether symptoms after gluten ingestion present or not, and severity of symptoms affected probability of compliance ○ Absence of immediate symptoms after ingestion described as option not to comply in socially inconvenient situations or because of sensory acceptance and/or lack GF foods ○ Also expressed doubts about compliance importance because of absence of immediate symptoms ○ Lack of knowledge gave rise to incorrect beliefs about CD and GFD, which sometimes explained noncompliance i.e. if adolescents were convinced that small amounts of gluten did no harm ○ Lack of GF alternatives was an excuse for noncompliance ○ For those who were concerned about following a GFD but found it difficult to abstain one solution was to choose alternative with the smallest amount of gluten ○ Curiosity about taste of food was another excuse for noncompliance ○ Felt that feelings of social inconvenience related to GFD could be avoided by eating normal food whereby

– **Bibliographic reference**	– **Olsson (2008): The everyday life of adolescent coeliacs: issues of the importance for compliance with the gluten-free diet**
	occasional noncompliance described as solution to 'feel like all the others'. • Noncompliers o Absence of immediate symptoms and lack of knowledge abot the importance of GFD for long-term health central to non-compliance decisions o Sensory qualities of GF foods seemed to have greater impact on compliance than availability – conviction that normal foods always taste better than GF foods and will choose the food with the most favourable taste. o Disease not become an integral part of their life and had not accepted their diagnosis o Belief that would comply better in the future i.e when had own kids and as consequence of impaired health they believed would arise in the future because of noncompliance
– Source of funding	– The study was funded by grants from Magnus Bergvall foundation, the Gastronomic academic foundation, and the Solstickan Foundation
– Comments	
– –	

– **Bibliographic reference**	– **Bystrom (2012): Health-related Quality of life in children and adolescents with celiac disease: from the perspectives of children and parents**
– Study type and aim	– Qualitative cross sectional study to examine how children and adolescents on GFD valued their HRQOL, and if age and severity of disease at onset affected children's self-valuation later in life. Parent's valuations of their child's life also assessed.
– Study quality	**CASP QUALITATIVE TOOL:** 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes

– **Bibliographic reference**	– **Bystrom (2012): Health-related Quality of life in children and adolescents with celiac disease: from the perspectives of children and parents**
	3. Was the research design appropriate to address the aims of the research question? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Not applicable 7. Has ethical issues been taken into consideration? Yes, the study has ethical consent 8. Was the data analysis sufficiently rigorous? Yes, normality was assessed and nonparametric statistics were used accordingly 9. Is there a clear statement of findings? Yes 10. How valuable is the research? Valuable –
– Number of patients	– N= 160 families with children 8 – 18 years
– location	–
– Patient characteristics	– **Inclusion criteria:** Children who visited south eastern paediatric clinics in Sweden for CD follow-up between 2006-2007. – **Exclusion criteria**: Children with comorbid diabetes, poor understanding of the Swedish language, or with cognitive difficulties – **Mean age**: 13 years (8 – 18) – **Mean age at diagnosis**: – **Mean years since diagnosis**: 10 years (1-17) – – In 9 of the participating families there were 2 children with CD
– Signs and symptoms	– N/A

– **Bibliographic reference**	– **Bystrom (2012): Health-related Quality of life in children and adolescents with celiac disease: from the perspectives of children and parents**
– Investigations	– DISABKIDS chronic generic measure (Swedish version) questionnaire • Child estimates QoL based on: o mental health; 4 Q's about independence: autonomy and ability to live without restrictions related to CD, and emotion (anxiety, anger, and worries) o social health; 2 Q's about social community, including acceptance and good relations with others; and 2 Q's about social exclusion o Physical health: Q's focused on functional limitations and physical health status. Also Q's on medical treatment which is of no relevance to this study. • Constructed to address chronically ill children between 8 – 18 years • Proxy version where parent estimates QoL of their child • Short term version used (is also a long term version not used here) • 5 point Likert scale scores each question where high represents high HRQoL. • At analysis, each question recoded from 1-5 points to 0-100 points, according to user's manual for DISABKIDS –
– Length of follow up	– N/A
– Outcome	• Resolution of symptoms • Patient experience • Complications of cd • Adherence • **Health related quality of life** • Impact on carers
– Results	– **Health related quality of life** – – Total score • Median value of children's score was 92 (85.5 – 96) o Mental health median value:85 points (75 – 95) o Social health median value 95 points (90 – 100)

– **Bibliographic reference**	– **Bystrom (2012): Health-related Quality of life in children and adolescents with celiac disease: from the perspectives of children and parents**
	○ Physical health median value 100 points (90 – 100) • Median value of parent's score was 85 (35 – 90) ○ Mental health median value:80 points (75 – 90) ○ Social health median value 95 points (90 – 100) ○ Physical health median value 100 points (20 – 100) – Correlations with HRQoL • Years since diagnosis correlated with QoL r = 0.26 • Age at diagnosis correlated with increased QoL 92 (88 -96) vs 85 (35 – 90) • Parents score for their child was lower than child's estimate: 86 (80 – 92) vs 92 (84 – 96). These were correlated r 0.43 •
– Source of funding	–
– Comments	
– Final response rate: 97.5% children (n=156), and 95% parents. (n=152): One child questionnaire was ruined and 3 parents visited clinic without their children. Eight adolescents visited the clinic without their parents, hence loss of parent data. –	

– **Bibliographic reference**	– **Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective** [d]
– Study type and aim	– Cross sectional study to evaluate difficulties experienced strategies used and emotional impact following GFD in those with CD
– Study quality	**CASP QUALITATIVE TOOL:**

[d] Same group as Rashid paper – cohort from Canadian celiac association

– **Bibliographic reference**	– **Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective** [d]
	1. Was there a clear statement of the aims of the research? Yes - aims clear 2. Is a qualitative methodology appropriate? YES 3. Was the research design appropriate to address the aims of the research question? Yes - standardised questionnaire 4. Was the recruitment strategy appropriate to the aims of the research? Yes - mailed to all members of CD society 5. Was the data collected in a way that addressed the research issue? yes 6. Has the relationship between researcher and participants been adequately considered? Not applicable 7. Has ethical issues been taken into consideration? Not applicable / unclear 8. Was the data analysis sufficiently rigorous? Yes - data was analysed and cross-analysed by 4 data clerks. Extraneous factors sufficiently controlled for. 9. Is there a clear statement of findings? Yes - data clearly outlined in tables 10. How valuable is the research? Valuable to inform specific Canadian CD population and wider general CD population on life on GFD and living with CD diagnosis and management. –
– Number of patients	– N = 5912 adults with biopsy-confirmed CD
– location	– Canada
– Patient characteristics	– **Inclusion criteria:** 10, 693 households with membership of CCA or FQMC were mailed questionnaire in 2008. Individuals >18 years following a GFD were eligible. A total of 7823 completed questionnaires – **Exclusion criteria**: of 7823 forms filled out, 436 were excluded because of: forms that were not filled out correctly (incomplete datasets), a further subset excluded due to no biopsy confirmation of CD. – **Mean age**: 56years (15.2) – **Mean age at diagnosis**: NA

– **Bibliographic reference**	– **Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective** [d]
	– **Mean years since diagnosis**: NA –
– Signs and symptoms	–
– Investigations	– QUESTIONNAIRE • Developed collaboratively between CCA and FQMC • 59 questions: demographics, diagnosis, symptoms, adherence, info sources, knowledge of GFD, emotional impact, difficulties, life situation (Leffler, 2009) • Difficulties, strategies, and emotions presented in questionnaire were identified in the scientific literature, by clinical experts, and finalised in consultation with psychometric experts. • Questions on usefulness of info sources, emotional impact, difficulties, and strategies were asked on a 5 point scale with options: never, rarely, sometimes, often, very often • Questionnaire mailed to 10 693 households of members of CCA and FQMC – total of 7823 were received • Emotion questions – respondents asked to report on emotions during the month before survey and their first recollections of the emotions experienced in first few months after diagnosis –
– Length of follow up	–
– Outcome	• Resolution of symptoms • **Patient experience** • Complications of cd • **Adherence** • Health related quality of life • Impact on carers
– Results	– **Adherence:** • 68% never intentionally consumed gluten • 18.8% had intentionally consumed gluten once or twice in previous year • Remaining 13.2% reported intentional consumption at least once a month in previous year. • percentage of respondents reporting intentional consumption was lower in those who had been following a GFD for a

– Bibliographic reference	– Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective [d]
	linger amount of time • 87.8% indicated considered preventing long-term complications and avoiding immediate reactions as being equally important in avoiding gluten • 9.9% preventing long term complications most important reason for adherence • 2.2% preventing reactions most important – Info about gluten • Obtained info about gluten free diet from various sources. Very good/exclellent sources indicated as follows: o Coeliac support association – 90%; another patient, 67%, cookbooks, 62%, internet 52%, dietician, 52%, medical books 51%, gastroenterologist 43%, magazing 28%, family doctors 25% – Knowledge about gluten • 49% able to ID item correctly on list of 15 foods the 7 no gluten foods. Further 32.5% correctly identified 6/7 items. • 38% people on GFD identified all 7 non allowed items vs 52% people on GFD >5 years – more knowledge longer follow diet. – – **Patient experience/complications from CD** – – Emotions associated with GFD • Emotions experienced often or very often in first few months after diagnosis compared to month before survey (overall population): o Relieved 58% vs 44% o Accepting 57% vs 70% o Frustrated 57% vs 21% o Overwhelmed: 49% vs 8% o Isolated: 42% vs 17% o Confused: 37% vs 6% o Anxious: 37% vs 6% o Sad: 34% vs 9% o Angry: 31% vs 9%

– Bibliographic reference	– Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective [d]
	○ Depressed: 23% vs 7% • All of these were highly significant in difference in score between months after diagnosis to present – – Difficulties experienced • 39 key difficulties identified: 12/39 experienced by a significantly higher % of women than men • Those on diet for >5 years experienced few difficulties overall • Most common difficulties experienced by all: ○ Limited food choices in restaurants: 88% ○ Concern that gluten not always on food labels:80% ○ High cost of GF foods : 61% ○ Not liking others to feel sorry for them: 66% ○ Worrying about cooks in restaurants not being trained in preparing GF meals: 64% ○ Lmited choices of food for lunches in school/work cafeteria: 85% ○ Variety of food-associated difficulties when travelling i.e not reading labels: 69% ○ 25% suspected their family and friends were afraid to invite them over for meals ○ Difficulty obtaining GF meals in hospital and retirement homes: 43% ○ Difficulty obtaining gluten content in drugs 36% ○ Limitations in religious practice: 25% ○ Feeling guilty on having passed CD onto children/grandchildren: 25% • Emotional difficulties: ○ I feel I am a burden – 34% ○ Im ambarassed about my diet: 27% ○ I avoid social events because of food: 32% ○ I feel neglected: 15% ○ I do not like others to feel sorry for me: 66% ○ People think a bit of gluten will not hurt me: 46% – Strategies used:

– Bibliographic reference	– Zarkadas (2012): Living with coeliac disease and a gluten-free diet: a Canadian perspective [d]
	• Strategies used by largest proportion of people included: • Reading every ingredient list – 96% • Using CCA pocket dictionary: 55% • Labelling all GF items (flours) – 84% • Storing GF foods in separate area: 75% • Enquiring about gluten in foods when out – 75% • Having snacks on hand at school and work – 78% • Talking to others about CD and GFD – 68% • If an event involves food, reminding others about my GFD : 58% • Taking translated information about the GFD when abroad – 44% • Overall, participants who reported a great number of strategies reported a reduced likelihood to intentionally consume gluten • This true between both men and women, but overall men used fewer strategies –
– Source of funding	– Funding provided from bureau of chemical safety, food directorate, health Canada, and the JA Campbell Research Fund of the Canadian Celiac association
– Comments	
– –	

– Bibliographic reference	– Cederborg (2011): Living with children who have Coeliac disease: a parental persepective
– Study type and aim	– Qualitative cross-sectional study: uses interpretative phenomenological approach to enhance the understanding of how to support family adjustment to a GFD

– **Bibliographic reference**	– **Cederborg (2011): Living with children who have Coeliac disease: a parental persepective**
– Study quality	**CASP QUALITATIVE TOOL:** 1. Was there a clear statement of the aims of the research? Yes - aim to understand impact on family of child with CD 2. Is a qualitative methodology appropriate? Yes - no other method applicable 3. Was the research design appropriate to address the aims of the research question? Yes - structured interview 4. Was the recruitment strategy appropriate to the aims of the research? NO - unclear recruitment. No mention of how participants were found or approached 5. Was the data collected in a way that addressed the research issue? Yes - thematic analyses of key interview themes undertaken 6. Has the relationship between researcher and participants been adequately considered? NO - unclear relationship between researcher and participant, and who analysed data 7. Has ethical issues been taken into consideration? Not applicable 8. Was the data analysis sufficiently rigorous? Yes - key themes thoroughly explored 9. Is there a clear statement of findings? Yes - thematic analyses and supportive quotes supplied in text 10. How valuable is the research? Valuable - limited information available to date on impact on family of having a child with CD. –
– Number of patients	– 20 parents of 14 children interviewed
– location	– Sweden
– Patient characteristics	– **Inclusion criteria:** families of which children who had a definite diagnosis of CD and had been livin with the disease and a GFD for at least 2 years. Among those that met inclusion criteria consecutively chose 15 families with a child diagnosed

– **Bibliographic reference**	– **Cederborg (2011): Living with children who have Coeliac disease: a parental persepective**
	with CD. All but one of the representatives consented to being interviewed. Interviewed in 3 groups: 1. First group: parents whose children performed their first small intestine biopsy (SIB) before 2 years of age (7 children, 13 parents) at time of interview children between 3 and 5 years 2. Second group parents whose children were >23 years when went through first SIB (3 parents and 3 children) 3. Third group: parents whose children had performed first SIB before 2 years of age but were older than first group at time of interview (16 years old) – **Exclusion criteria**: None listed – **Mean age**: group 1: 4.3 years; group 2: 16.3 years, group 3: 16 years – **Mean age at diagnosis**: NA – **Mean years since diagnosis**: NA –
– Signs and symptoms	– NA
– Investigations	– Interview: • Interview took place in home • Recorded all interviews and used semi-structured interview guide that includes open ended questions about how parents experienced their children's disease • Depending on parents answers, asked follow-up questions to obtain a deeper understanding of their experiences • Transcribed verbatim and exhaustively examined for references to similarities and differences • Then identified sections of the text that illustrate how parents experience their children's disease before and after diagnosis and how manage to adopt a GFD • Then chose among the examples to find those that most obviously captured participants' thoughts and beliefs
– Length of follow up	–
– Outcome	• Resolution of symptoms • **Patient experience** • Complications of cd • Adherence • Health related quality of life

– **Bibliographic reference**	– **Cederborg (2011): Living with children who have Coeliac disease: a parental persepective**
	• **<u>Impact on carers</u>**
– Results	– Organized results into 2 categories with subthemes: 1) struggle to understand child's disease before the diagnosis; 2) process of transforming to a GFD – – Struggle to understand disease • Mother of a 5 year old boy suspected something was wrong with her son when she tried to give him ordinary food – " when we gave him ordinary food hejust cried…he bawled through meals" • 5 year old lost weight dramatically – " she lost more than a kilo so she was really weak. It was terrible" • One parent did not suspect. Her child was coincidentally tested with no symptoms – " she never showed any symptoms, she had never been sick" • Parents described process of gaining understanding among HC professionals before the diagnosis as a 'struggle' and concerns not taken seriously • Mother 4 year old, 5 months to diagnosis. Staff at well-baby clinic told her not to worry – " I felt everything was not as it should be. They went against me many months before the diagnosis was made. Now looking back, I regret I did not stand my ground more than I did or go to a private doctor". • Most of parents said they were relieved when they knew what was wrong with their child • Mother 4 year old girl – "it was wonderful to get the diagnosis. It was a relief" • Getting diagnosis meant parents knew how they could help their child to reduce symptoms – – Transforming to a GFD • Most parents reported rapid normalization process to a GFD. • One mother of 2 year of said was confused for about 2 months after diagnosis – "I panicked about everything…the first 2 months were a mess. • Parents express appreciation of child's response to GFD – "as she gets older she is more aware of this" • Mother 17 year old who got diagnosis as teen said harder for her child – "it might be different if she got sick as soon as she ate gluten food. Theyn you know you cannot eat this because you will get sick and not feel well afterwards" • Parents whose children were diagnosed when young have had opportunity to socialize their children into a GFD. These children usually haven't experienced taste of gluten food and were not aware of what they are missing.

– **Bibliographic reference**	– **Cederborg (2011): Living with children who have Coeliac disease: a parental persepective**
	• Mother of 5 year old could not stop worrying about what woud happen if her daughter tasted something she should not eat – 2 it is always ther that she could get access to crumbs” • Most parents reported seldom visited restaurants for reason such as not trusting staff’s description of ingredients or lack fo food for child • One parent spoke of restricted leaisure activities for her 16 year old son – “ he cannot spontaneously be with his oeers, everything has to be checked and questioned if he eats with them, I think he fears his peers will think he is a bother to be with. I think the disease hinders him socially” • Parents said travelling could be demanding because of difficulties getting acces to propoer food • Visiting houses can be difficult. One parent always called house before to check food and make soue would be GF food available • Expressed struggle to get staff at daycare and school to understand their childrens GFD • Daycare staff not sufficiently educated • Negative attitudes from staff at school’s dining hall • Parents actively and constantly try to find out as much as possible about the disease and how to meet childs GFD needs. • Aprents of a 3 year olf search for knowledge through people who know about the disease, on the internet, and through the CD association • Most parents have regular contact with a dietician • Parents have concerns for children’s future. • Mother of 5 year olf worries about how child will cope when living alone • Parents put hope into new treatments based on scientific breakthroughs
– Source of funding	– Swedish society for coeliacs, FORSS and the Swedish research council
– Comments	
– –	

– **Bibliographic reference**	– **Bellini (2011): Compliance with the gluten-free diet: The role of locus of control in celiac disease**
– Study type and aim	– Case-control study to verify whether subjects with CD have a different locus of control (LoC) compared with healthy subjects, and to evaluate relationship between LoC and compliance with GFD and quality of life
– Study quality	**CASE - CONTROL STUDY > USE QUADAS**
– Number of patients	– N = 509: 156 CD patients on GFD and 353 healthy controls
– location	– Italy
– Patient characteristics	– **Inclusion criteria:** CD group: biopsy-proven patients with CD diagnosed using ESPGHAN criteria. Recruited at children's hospital during follow-up visits in patients ho had been on a GFD for at least a year. HC group: controls without chronic disease who were aattending school in Trieste, Italy. – **Exclusion criteria**: none listed – **Mean age**: CD patients = 10 years; HC = 12 years – **Mean age at diagnosis**: 6.4 years – **Mean years since diagnosis**: na –
– Signs and symptoms	– na
– Investigations	– Questionnaires – Nowicki-Strickland Locus of control scale (NSLCS) and QoL questionnaire filled out with help of 2 investigators blinded to subject data. Beforehand, detailed explanation of study was given to each child's parents, and informed consent was obtained. – – NSLCS: • Children aged 6-8 completed preschool and primary school version which contained 13 items • Children 9 – 16 completed 40 item test • Both consist of Y/N questions ie. "are some ids born lucky"; "Do you feel that most of the time it doesn't pay to try hard because things never turn out right anyway?" and "most of the time, do you feel that you can change what might happen tomorrow by what you do today?"

– **Bibliographic reference**	– **Bellini (2011): Compliance with the gluten-free diet: The role of locus of control in celiac disease**
	• LoC values calculated following NSLCS manual instructions • High score indicates externality and low LoC; low score indicates high LoC and internality – QoL • To evaluate QoL and GFD compliance, version of Kindl test modified for children withCD • 40 item questionnaire assessing 4 domains of QoL: Psych well-being, social relationships, physical function, everyday life activities in chiroically ill children • Modified version comtained 10 items that measure subjective well being • noncompliance with GFD was defined as findings positive TTG on serology assay or patient's self-reported transgressions
– Length of follow up	– N/A
– Outcome	• Resolution of symptoms • **Patient experience** • Complications of cd • **Adherence** • **Health related quality of life** • Impact on carers
– Results	– Adherence: • At follow-up 34/156 patients defined as noncompliant with GFD after admission of monthly transgressions (ave 3 pm), especially during social occasions. Of these, 12/34 had positive IgA tTG – – LoC and QoL • CD patients with good compliance to GFD had lower levels of LoC score and higher internality than those with poor compliance (5 +/- 1.9 vs 5.1 +/- 2.0)in younger patients with CD p=0.8 • CD patients with good compliance to GFD had lower levels of LoC score and higher internality than those with poor compliance (12.6 +/-4.2 vs 25.2 +/-3.6) in older patients with CD, p = 0.01 • CD patients who reported satisfcatory QoL (127/156) had lower LoC values than those who perceived their life as negatively affected by the disease (4.7 +/-1.7 vs 6.1 +/-) in younger children and (12.6 +/- 4.0 vs 16.3 +/- 4.0) in older

– **Bibliographic reference**	– **Bellini (2011): Compliance with the gluten-free diet: The role of locus of control in celiac disease**
	patients with CD.
– Source of funding	– Supported by grant 36/08 from institute of child health IRCCS “Burlo Garofolo”
– Comments	
– –	

– **Bibliographic reference**	– **Leffler (2008): Factors that influence adherence to a gluten-free diet in adults with celiac disease**
– Study type and aim	– Qualitative cohort study to determine factors that influence GFD adherence in cohort of CD patients
– Study quality	**CASP QUALITATIVE TOOL:** 1. Was there a clear statement of the aims of the research? Yes - objecective to identify factors influencing GFD adherence in adults with CD clearly stated 2. Is a qualitative methodology appropriate? Yes - survey design appropriate 3. Was the research design appropriate to address the aims of the research question? Yes, questionnaire carefully devised with range of experts from different areas within the field. 4. Was the recruitment strategy appropriate to the aims of the research? Yes - all eligible participants approached 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Not applicable

– **Bibliographic reference**	– **Leffler (2008): Factors that influence adherence to a gluten-free diet in adults with celiac disease**
	7. Has ethical issues been taken into consideration? Yes - informed consent taken before research 8. Was the data analysis sufficiently rigorous? Yes. Statistical methodology clearly outlined 9. Is there a clear statement of findings? Yes - findings clearly outlined 10. How valuable is the research? Valuable as large multicentre study with thorough questioning in multiple domains –
– Number of patients	– N = 154
– location	– USA
– Patient characteristics	– **Inclusion criteria:** adults diagnosed with biopsy-confirmed CD for longer than 3 months were elisted through recruitment posters that were mailed to New England support groups and adverstisements placed in regional CD newsletters and publications frequented by CD patients. In addition, eligible patients with CD being treated at Celiac centre at MIDMC were invited to participate – **Exclusion criteria**: – **Mean age**: 50 years – **Mean age at diagnosis**: 45 years – **Mean time on GFD:** 58 months –
– Signs and symptoms	–
– Investigations	– Expert panel assembled to identify factors perceived to be important in living with CD and influential in GFD adherence – Set of domains relevant to life with CD were elucidated – These included: psychosocial burden of disease; symptoms; social and health support; self-efficacy; perceived adherence; general health – Bank of items developed to assess these – Items were assessed for clarity and comprehensiveness by 2 successive focus groups of 8 – 12 adults with biopsy-confirmed CD into the final questionnaire – Final questionnaire = global celiac assessment scale (GCAS) – 142 items

– **Bibliographic reference**	– **Leffler (2008): Factors that influence adherence to a gluten-free diet in adults with celiac disease**
– Length of follow up	– N/A
– Outcome	• Resolution of symptoms • Patient experience • Complications of cd • **Adherence** • Health related quality of life • Impact on carers
– Results	– Adherence: – • Population found to adhere well to GFD with 44% (test) and 34% (clinic patients) rated as excellent or good by expert nutritionist. • Tended to overestimate adherence as 70% reported to be strict adheres • Married participants more adherent than unmarried • Significant correlations between CGAS items and adherence • 75% did not feel cost made it difficult to adhere • 51% reported cost important issue in living with CD • 56% reported finding GF foods when eating outside of home • 75% rated quality of GF foods a significant concern • 75 – 79% reported believed accidental and purposeful consumption of gluten had important health ramifications • 44% reported excellent understanding of the GFD • 46% reported good understanding of GFD • 16/28questions correct in adheres on GFD knowledge test vs 14/28 in poor adherers • 75% reported were able to follow a GFD when travelling • 24% avoided travel due to food restictions • 82% able to follow GFD at social events and parties • 21% avoided social engagement involving food

– **Bibliographic reference**	– **Leffler (2008): Factors that influence adherence to a gluten-free diet in adults with celiac disease**
	• Only 45% felt were able to follow GFD in religious practice and 37% reported avoiding certain religious practices to maintain a GFD • 59% belonged to CD association and of these 8&% felt this was beneficial • 75% reported felt comfortable following GFD at work • Reported receiveing adequate support form HC providers: dietician 63%; gastro 57%; GP 36%; pharmacist 22% • 41% reported keeping GFD increased stress • 33% reported following GFD to have negative effect on social life • 62% being diagnosed positively affected their life • 96% avoided gluten from worry of long term consequences • 84% avoided gluten to avoid symptoms
– Source of funding	– Charitable dontations to celiac centre at BIDMC, the celiac sprue association, NIH T32 training grant, and the Harvard –Thorndike general clinical research center M01 RR01032
– Comments	
– –	

– **Bibliographic reference**	– **Jacobssen (2007)**
– Study type and aim	– RCT to assess benefit of ‘celiac school’ educational program for women with CD to improve GI symptoms
– Study quality	– **NICE RCT quality checklist:** –

– **Bibliographic reference**	– **Jacobssen (2007)**
	1. Was an appropriate randomisation method used? UNCLEAR - randomisation carried out locally by primary author according to town of residence using consent forms as lots. What does this mean? Unclear whether author was blinded. If randomised according to residence, unclear whether it was pseudo or complete random allocation 2. Was there adequate concealment of allocation? Not applicable 3. Were groups comparable at baseline? Yes. Groups comparable in all domains at baseline, except I the domain of abdominal pain 4. Did the comparison groups receive the same care apart from the intervention of interest? Yes - waitlist control so controls received nothing and intervention group received intervention only 5. Were participants receiving care kept blind to their treatment allocation? Not applicable 6. Were individuals administering care kept blind to treatment allocation? Not applicable 7. Were all groups followed for equal amount of time? Yes - all groups had same follow-up of 10 weeks. 8. Were groups comparable for treatment completion? NO - intervention group had higher rate of completion than waitlist control 9. Were groups comparable with respect to availability of outcome data? Yes 10. Did the study have an appropriate length of follow-up? Yes - 10 weeks seems appropriate as is an experimental intervention. 11. Did the study use a precise definition of outcome? 12. Did the study use a valid and reliable method to determine outcome? NO - 2 x pairwise regression models used. A multiple regression examining the treatment x group interaction would have been preferable and more statistically stringent. Presumably this interaction was non-significant and they have not reported this. 13. Were investigators kept blind to participant's exposure to intervention? NO - unclear whether investigators blinded 14. Were investigators kept blind to other confounding and prognostic factors? NO - unclear whether investigators blinded LOW QUALITY: Randomisation unclear, level of blinding of experimenters to exposure to intervention or other confounding factors unclear, Statistical methods are not sound and show only a turned towards a statistical effect as no significant group x intervention interaction was found
–	– N = 105 (n=54 intervention group; n=52 in control group)
– location	– Sweden

– **Bibliographic reference**	– **Jacobssen (2007)**
– Patient characteristics	– **Inclusion criteria:** women from 5 hospitals in southeast Sweden with a diagnosis of celiac disease. Diagnosis must be based on histology showing findings compatible with CD, female gender, aged 20+ years, a history of GFD for a minimum of 5 years – **Exclusion criteria**: None listed – **Mean age**: 23 – 80 years – **Mean age at diagnosis**: – **Mean years since diagnosis**: –
– Signs and symptoms	– Indigestion – Diarrhea – Constipation – Abdominal pain – Reflux –
– Investigations	• Education program. • Women randomised to each arm, educational school for celiacs, or sent leaflets at home • 3 main features emphasized in education program : o Working in small groups o Starting from real-life situations o Using a problem-solving process that stimulated self-directed learning • Celiac school: o 10 sessions that included weekly meetings in groups 7 – 9 persons o Each tutor was familiar with problem based learning (PBL) pedogogy and acted as moderator o Main purpose of program was to support and encourage participants to find possible changes in lifestyle and thereby reduce GI symptoms and achieve knowledge in the area o 7 intervention groups set up in 5 cities o Each session covered pre-determined specific topic: anxiety and fears associated with CD; attitudes to surroundings, psychological reactions, coping strategies, obstacles in daily life, new knowledge, and various

– **Bibliographic reference**	– **Jacobssen (2007)**
	questions associated with food and cooking. o With this as starting point, group members decided what to discuss together on basis of specific needs and desires that came to light after the inventory • Controls o Received total of 5 circulars by post over a 10 week period o These contained written info o The info covered evidence-based details on CD o Brochures dealing with origins, symptoms, diagnosis, and treatment concerning CD and info about current research in the area
– Length of follow up	– 10 weeks and 6 months after completing education
– Outcome	• **Resolution of symptoms** • Patient experience • Complications of cd • Adherence • Health related quality of life • Impact on carers
– Results	– GI symptoms • Difference in total mean index value regarding GI symptoms between groups at baseline where control patients reported slightly fewer symptoms • After 10 weeks total mean index value was not significantly different between the groups at 10 weeks • Comparison within intervention group between baseline and 10 week follow up showed significant impriovement in total GI score, particularly for: • Constipation • Abdominal pain • Total index improvement also showed significant improvement after 6 months in comparison to baseline with general improvmen in all dimensions except reflux. • Comparison between changes in mean scores within intervention group and control group from baseline to 10 weeks

– **Bibliographic reference**	– **Jacobssen (2007)**
	showed statistically significant difference in improvement regarding abdominal pain, but there was no significant difference regarding other clinical symptoms or the GI total index
– Source of funding	– Medical research council of southeast Sweden and the Ostergotland country council

D.14 Review question 7.3

Bibliographic reference	**Hallert (2009)** **Ref ID: 347**
Study type	RCT (method of randomisation not reported)
Study quality	Low quality
Number of patients	Total = 65; Intervention = 33, Placebo = 32
Patient characteristics	**Inclusion criteria:** Diagnosis based on histology showing findings compatible with CD, age 45–64 years, a history of being on a GFD for at least 8 years and evidence of remission. *Note: Absence of serum IgA tissue transglutaminase (tTG) antibodies and asymptomatic DH controlled by diet alone were accepted as evidence of remission.* **Exclusion criteria:** Concomitant serious disorder, positive serology for CD, any B vitamin supplementation within 3 months of inclusion, pharmacological doses of vitamin B-12, folic acid or pyridoxine (vitamin B-6) within 3 years of inclusion, ongoing therapy with drugs known to influence plasma total tHcy levels, resection of terminal part of the small intestine, hypersensitivity to B vitamins and assumed inability to comply with the study protocol. **Baseline characteristics:**

	Intervention (n=33)	**Placebo (n=32)**
Male/Female	14/19	10/22
Withdrawals	5/33	5/32
Per-protocol analysis	n=28	n=29

<table>
<tr><th>Bibliographic reference</th><th>Hallert (2009)
Ref ID: 347</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Intervention (n=28)</td><td>Placebo (n=29)</td></tr>
<tr><td>Baseline P-tHcy (µmol／L) [median and range]</td><td>11.7 (7.8 to 23.0)</td><td>11.4 (7.4 to 21.9)</td></tr>
<tr><td></td><td>Intervention (n=11)</td><td>Placebo (n=12)</td></tr>
<tr><td>Baseline PGWB index [median and range]</td><td>89 (76 to 98)</td><td>90 (43 to 99)</td></tr>
</table>
Note: for PGWB index, data only available for analysis: Intervention (n=11); Placebo (n=12)
</td></tr>
<tr><td>Intervention</td><td>A daily dose of 0.8 mg folic acid, 0.5 mg cyanocobalamin (vitamin B-12) and 3 mg pyridoxine (vitamin B-6)</td></tr>
<tr><td>Comparison</td><td>Placebo for 6 months</td></tr>
<tr><td>Length of follow up</td><td>6 months (end of intervention)</td></tr>
<tr><td>Location</td><td>The patients recruited into the study had been diagnosed with CD at four hospitals in Sweden in 1974–95 after showing a flat or nearly flat intestinal mucosa that improved on a GFD as stated in the medical records.</td></tr>
<tr><td>Outcomes measures and effect size</td><td>The outcome measures were psychological general well-being (PGWB) and the plasma total homocysteine (tHcy) level, marker of B vitamin status.

<u>P-tHcy (µmol／L) [median and range]:</u>
Baseline: Intervention = 11.7 (7.8-23.0); placebo = 11.4 (7.4-21.9)
At 6-month: Intervention = 7.9 (5.0-11.3); placebo = 11.1 (5.3-22.4), p<0.001
(also significant between baseline and 6-month for the intervention group only, p<0.001)

<u>PGWB index [median and range]:</u>
Baseline: Intervention = 89 (76-98); placebo = 90 (43-99)
At 6-month: Intervention = 105 (87-115); placebo = 94 (40-121), p > 0.05 (ns)
(only significant between baseline and 6-month for the intervention group only, p<0.01)

The upper reference limit for plasma tHcy was set at 15.6 µmol／L using the 95th percentile of a local population sample (n = 65) representing age- and gender-matched general population controls.</td></tr>
<tr><td>Source of funding</td><td>None reported.</td></tr>
</table>

Bibliographic reference	**Hallert (2009)** **Ref ID: 347**
Comments	No mention of allocation concealment and not reported the method of randomisation. Imprecise effect estimates due to small sample size with high number of withdrawals. Only conducted per-protocol analysis (no ITT). Study population only comprised of middle-aged adults living in Sweden. The design of the study was unable to clarify which B vitamins were connected with the study outcomes.
Authors' own conclusion: Adults with longstanding coeliac disease taking extra B vitamins for 6 months showed normalized tHcy and significant improvement in general well-being, suggesting that B vitamins should be considered in people advised to follow a gluten-free diet.	
Bibliographic reference	**Hogberg (2004): Oats to children with newly diagnosed coeliac disease: a randomised double blind study** **Reference ID: 367** **Hollen (2006a): Coeliac children on a gluten-free diet with or without oats display equal anti-avenin antibody titres** **Reference ID: 603** **Hollen (2006b): Urinary nitric oxide during one year of gluten-free diet with or without oats in children with coeliac disease** **Reference ID: 559** ***Note: multiple publications of the same study***
Study type	RCT
Study quality	Low quality
Number of patients	Total = 116 children; GFD with oats = 57, standard GFD = 59 Withdrawals and lost-to-follow up: GFD with oats = 15 withdrawn (6/15 withdrawn due to suspected intolerance to study diet), no lost to follow-up Standard GFD = 7 withdrawn (2/7 withdrawn due to suspected intolerance to study diet), 2 lost to follow-up Per-protocol analysis (GFD with oats = 42, standard GFD = 50)
Patient characteristics	**Inclusion criteria:** Children with 'newly diagnosed' symptomatic CD, willingness to participate, aged less than 18 years, small bowel biopsy showing enteropathy, and a good understanding of the Swedish language. **Baseline characteristics:**

Bibliographic reference	Hallert (2009) Ref ID: 347
	• Mean age = 6.5 years (SD 4.6; median 6.0; range 8 months–17.5 years). • Children less than 2-year old (PP) = 20/42 (GFD with oats); 12/50 (standard GFD) • The male/female distribution was equal in the two groups (1.0/1.4). • 7 children had diabetes mellitus (3 in the GFD-oats group; 6 had IgA deficiency only one of them in the GFD-oats group. The only patient with Down's syndrome had GFD without oats).
Intervention	GFD with oats (aimed at a daily oat intake of 25–50g) • The oats used were specially grown, milled, and packaged so as not to become contaminated with wheat, rye, or barley. The oat products were tested by an ELISA assay to ensure absence of gluten contamination.
Comparison	Standard GFD
Length of follow up	12-month study period (the parents of each study patient were requested to monitor the daily intake of study products for the first month of the diet and thereafter for one week immediately prior to visits to the clinic at 3, 6, 9, and 12 months, respectively).
Location	8 Swedish paediatric clinics in Norrkoping, Linkoping, Motala, Vastervik, Vastera°s, Orebro, Stockholm (Sachsska Hospital), and Goteborg, between April 1998 and September 2001.
Outcomes measures and effect size	Blood samples were taken at 0, 3, 6, and 12 months. Sera were stored at 220°C pending analysis. IgA antigliadin antibody (AGA), antiendomysium antibody (EMA), and antitissue transglutaminase (TGA) titres were measured. Total IgA titre was also measured. When a low IgA value was found, measurement of IgG EMA titre was also done. After approximately one (mean 1.1 years; range 0.9–1.5) year on the GFD with or without oats, a small bowel biopsy was done to assess healing of the mucosa. No ITT, only per-protocol analysis (GFD with oats = 42, standard GFD = 50) In the GFD-oats group, due to some children consumed very small amounts of oat products towards the end of the study year, the GFD-oats patients were further divided into two subgroups according to the amount of oats ingested at the end of the study year: children taking at least 8 g of oats daily (n=34) and children taking less than 8 g daily (n=8). **Outcomes (at 12-month):**

Bibliographic reference	Hallert (2009) Ref ID: 347
	• Enteropathy: GFD-oats (all) = 0/42, GFD-oats ≥8g = 0/34, standard GFD = 2/50, RR (N/A), p>0.05 • Mean IEL count (per 100 enterocytes) (SD): GFD-oats (all) = 16 (4.5), GFD-oats ≥8g = 16 (4.0), standard GFD = 16 (5.0); $p_{(all\ vs.\ std)}$ = 0.84, $p_{(≥8g\ vs.\ std)}$ = 0.94 • IgA EMA positive: GFD-oats (all) = 14/42, GFD-oats ≥8g = 12/34, standard GFD = 12/50 *[$RR_{(oat\text{-}all\ vs.\ std)}$ = 1.39 (95%CI: 0.72 to 2.67); $RR_{(oats≥8g\ vs.\ std)}$ = 1.47 (95%CI: 0.75 to 2.88)]* • IgA EMA titres 1:10-1:20: GFD-oats ≥8g = 5/34, standard GFD = 8/50, RR = 0.92 (95%CI: 0.33 to 2.57) • IgA EMA titres 1:40-1:80: GFD-oats ≥8g = 7/34, standard GFD = 4/50, RR = 2.57 (95%CI: 0.82 to 8.12) • TGA positive: GFD-oats (all) = 7/42, GFD-oats ≥8g = 7/34, standard GFD = 5/50 *[$RR_{(oat\text{-}all\ vs.\ std)}$ = 1.67 (95%CI: 0.57 to 4.87); $RR_{(oats≥8g\ vs.\ std)}$ = 2.06 (95%CI: 0.71 to 5.95)]* • Median TGA titres (range): GFD-oats ≥8g = 7.0 (5.1-11.0), standard GFD = 12.0 (5.7-15.0), p=0.04 **Other serological outcomes (at 12-month):** *Optical density values (in relation to a high antibody level reference serum):* *Median IgA anti-avenin antibodies (range):* GFD-oats [n=38] = 0.24 (0.06 to 1.89), standard GFD [n=43] = 0.18 (0.01 to 1.05); p = 0.13 *Median IgG anti-avenin antibodies (range):* GFD-oats [n=38] = 0.93 (0.38 to 1.55), standard GFD [n=45] = 1.08 (0.51 to 1.62); p = 0.26 *Nitric oxide (NO) metabolites in morning urine as indicator of ongoing inflammation in the small intestine (the cut-off value = 1406 µM):* *Number of children above the cut-off value at 12-month:* GFD-oats = 9/34, standard GFD = 8/41; RR = 1.36 (95%CI: 0.59 to 3.13)
Source of funding	The Cerealia Foundation R&D, the Health Research Council in the South-East of Sweden, Swedish Nutrition Foundation, the

Bibliographic reference	**Hallert (2009)** **Ref ID: 347**
	Swedish Medical Society, Semper AB, the Va°rdal Foundation, the Odd Fellow Foundation, and Pharmacia Diagnostics, Sweden.
Comments	• Methods of randomisation not reported, blinding achieved by mixing oats were with otherwise gluten free products, such as mixes for formula, porridge and bread, baked ready-made bread, and cookies. • High number of withdrawals from the GFD with oats group due to intolerance to the diet, hence, bias towards underestimating the effect estimates. • No ITT analysis, different PP analyses were conducted. • Only 12-month follow-up, lack of data on long-term consequences.
Author's conclusion: This is in accordance with the findings of studies in adult coeliacs and indicates that oats, added to the otherwise GFD, can be accepted and tolerated by the majority of children with CD.	

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
Study type	RCT
Study quality	Low quality
Number of patients	In remission: Total = 52; oat-group = 26, control-group = 26 Newly diagnosed: Total = 40; oat-group = 19, control-group = 21

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
	Withdrawals (total = 11): *In remission group:* Oat-group = 3 (worsening of itching x 2, abdominal symptoms x 1) Control-group = 3 (worsening of itching x 1, withdrew without reason x 2) *Newly diagnosed group:* Oat-group = 3 (abdominal symptoms x 1, withdrew without reason x 2) Control-group = 2 (worsening of itching x 1, withdrew without reason x 1) **At 5-year follow-up (merged in remission group and newly diagnosed group):** Total = 63; oat-group = 35, control-group = 28
Patient characteristics	*Inclusion criteria (in remission group):* • 18 years of age or older and have normal or almost normal duodenal villous architecture while eating a gluten-free diet for at least 12 months (the original diagnosis of coeliac disease was based on the presence of subtotal or total villous atrophy of the duodenal mucosa before the introduction of the gluten-free diet). *Inclusion criteria (newly diagnosed group):* • All new adult patients with subtotal or total villous atrophy diagnosed (biopsy confirmed) at the Kuopio University Hospital between 1 December 1988 and 1 December 1990, were included in the study.

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
	Exclusion criteria (for both in remission and newly diagnosed groups): • Previous or current corticosteroid therapy; a history of complications of coeliac disease; any neurologic, cardiovascular, pulmonary, metabolic, hematologic, or endocrine disorder that could hinder participation; a history of drug or alcohol abuse; mental impairment; lack of cooperation; and refusal to take part. • Patients were also excluded if their diagnosis was not definite (e.g. if there was any other reason for villous atrophy such as cancer, previous irradiation, collagenous disease, or inflammatory bowel disease. • Patients who already consumed oats. **Baseline characteristics:** <u>*In remission group*</u> Gender (men/women): oat-group = 9/17 ; control-group = 8/18 Mean age (years) (SD): oat-group = 48 (12) ; control-group = 42 (10) Baseline mean (SD) symptom score (flatulence, abdominal pain and distention, general well-being): oat-group = 15.6 (13.7) ; control-group = 24.9 (23.1) Baseline mean (SD) villous atrophy grade (histopathological grade): oat-group = 0.57 (0.43) ; control-group = 0.54 (0.39) <u>*Newly diagnosed group*</u> Gender (men/women): oat-group = 7/12 ; control-group = 5/16 Mean age (years) (SD): oat-group = 42 (14) ; control-group = 48 (11) Baseline mean (SD) symptom score (flatulence, abdominal pain and distention, general well-being): oat-group = 35.3 (20.2) ;

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
	control-group = 26.6 (21.4) Baseline mean (SD) villous atrophy grade (histopathological grade): oat-group = 1.85 (0.68) ; control-group = 1.89 (0.65) **At 5-year follow-up (merged in remission group and newly diagnosed group):** Gender (male/female): oats-group = 13/22; control-group = 10/18 Mean age (SD): oats-group = 53 (12) years; control-group = 52 (10) years. Mean (SD) duration of the gluten free diet: oats-group = 10 (7) years; control-group = 10 (6) years Mean (range) intake of oats: oats-group = 34 (10–70)g/day. Compliance with strict-GFD: oats-group = 25/35 (71.4%); control-group = 22/28 (78.6%)
Intervention	The oat group received products supplemented with oats (2 types of gluten-free wheat-starch flour mixed with an equal amount of oats, muesli containing 60 percent oats, and rolled-oat breakfast cereal). The goal for the daily intake of oats was 50g to 70g. *Mean oat intake per day (SD):* *At 6-month: In remission group = 49.9g (14.7g); Newly diagnosed group = 43.6g (11.3g)* *At 12-month: Newly diagnosed group = 46.6g (13.3g)* *21 (81%) of the patients in remission and 14 (74%) of the patients with newly diagnosed disease were consuming more than 30 g of oats per day by the end of the study.*
Comparison	Control group received gluten-free cereal products (a mixture of low-protein flours containing 0.74 mg of gluten per gram of

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	foodstuff).
Length of follow up	6-month for the in remission group; 12-month for the newly diagnosed group; 5-year follow-up for a subgroup of patients
Location	The Kuopio University Hospital, Finland, between 1 Dec 1988 and 31 Dec 1990
Outcomes measures and effect size	Villous atrophy was graded as 1 = partial; 2 = subtotal; or 3 = total. A grade of 0 indicates the absence of villous atrophy. **Villous atrophy (mean histopathological grade)** *Mean change from baseline (SD):* In remission group (at 6-month) Oat-group = 0.01 (0.36) ; control-group = -0.06 (0.31); p=0.53 Mean change differences between groups = 0.07 (95%CI: -0.12 to 0.26) Newly diagnosed group (at 12-month) Oat-group = -1.07 (0.58) ; control-group = -1.20 (0.42); p=0.74 Mean change differences between group = 0.13 (95%CI: -0.23 to 0.43) **Symptom score (flatulence, abdominal pain and distention, general well-being)** (average of the 4 variables, each variable measured on a 100-mm scale, ranging from 0 = no symptoms at all; to 100 = extremely severe symptoms) *Mean change from baseline (SD):* In remission group (at 6-month)

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
	Oat-group = 6.7 (17.5) ; control-group = 2.1 (10.8); p=0.45 Mean change differences between groups = 4.6 (95%CI: -3.5 to 12.8) Newly diagnosed group (at 12-month) Oat-group = -8.2 (26.6) ; control-group = -8.4 (22.7); p=0.78 Mean change differences between groups = 0.2 (95%CI: -15.6 to 16.0) **Anti-gliadin IgA (EU/ml)** In remission group (at 6-month) Median (range) change from baseline: Oat-group = 0.0 (-0.47 to 0.41); control-group = 0.0 (0.0 to 0.39); p=0.33 Newly diagnosed group (at 12-month) Median (range) change from baseline: Oat-group = -0.73 (-0.99 to 0.00); control-group = -0.57 (-9.38 to 0.00); p=0.69 **Anti-gliadin IgG (EU/ml)** In remission group (at 6-month) Median (range) change from baseline: Oat-group = 0.0 (-1.21 to 2.02); control-group = 0.0 (-2.63 to 0.86); p=0.12 Newly diagnosed group (at 12-month)

Bibliographic reference	**Janatuinen (1995): A comparison of diets with and without oats in adults with coeliac disease** **Reference ID: 1122** **Janatuinen (2000): Lack of cellular and humoral immunological responses to oats in adults with coeliac disease** **Reference ID: 957** **Janatuinen (2002): No harm from five year ingestion of oats in coeliac disease** **Reference ID: 375** **Kemppainen (2007): No observed local immunological response at cell level after five years of oats in adult coeliac disease** **Reference ID: 548** ***Note: multiple publications from the same study***
	Median (range) change from baseline: Oat-group = -7.09 (-29.85 to 0.00); control-group = -2.99 (-55.2 to 0.53); p=0.99 **Anti-reticulin IgA (EU/ml)** <u>In remission group (at 6-month)</u> Median (range) change from baseline: Oat-group = 0.0 (-50.0 to 0.00); control-group = 0.0 (-50.0 to 0.00); p=1.00 <u>Newly diagnosed group (at 12-month)</u> Median (range) change from baseline: Oat-group = -200.0 (-2000.0 to 0.00); control-group = -175.0 (-4000.0 to 5.00); p=0.79 **Intraepithelial lymphocytes (IEL) count/100 epithelial cells** <u>In remission group (at 6-month)</u> Mean (SD) change from baseline: Oat-group = -0.6 (21.8); control-group = 2.0 (11.7); p=0.94 Mean change differences between group = -2.6 (95%CI: -12.3 to 7.2) <u>Newly diagnosed group (at 12-month)</u> Mean (SD) change from baseline:

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	Oat-group = -23.8 (23.3); control-group = -21.7 (14.5); p=0.84 Mean change differences between group = -2.1 (95%CI: -14.4 to 10.2) **<u>At 5-year follow-up (merged in remission group and newly diagnosed group):</u>** Total = 63; oat-group = 35, control-group = 28 **Villous atrophy (mean histopathological grade)** *<u>Mean change from 6-12month (SD):</u>* Oat-group = -0.55 (0.54) ; control-group = -0.52 (0.45); p=0.54 Mean change differences between groups = 0.03 (95%CI: -0.29 to 0.23) **Local cellular immunological responses at 5-year follow-up** (Data only available for oat-group = 22, control-group = 20) Median CD3+: Oat-group = 47; control-group = 47; p=0.51 Median αβ+: Oat-group = 20; control-group = 30; p=0.23 Median γδ+: Oat-group = 14; control-group = 16; p=0.90
Source of funding	Supported by grants from the Yrjö Janhsson Foundation and the Finnish Gastroenterological Association. The oat products were supplied by Raisio Factories, Melia, Raisio, Finland.

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Comments	• Randomisation according to gender, with allocation concealment and assessors blinded. • ITT analysis was conducted. • Small sample size.
Author's conclusion: Moderate amounts of oats can be included in a gluten-free diet for most adult patients with coeliac disease without adverse effects.	

Bibliographic reference	**Peraaho (2004): Effect of an Oats-Containing Gluten-free Diet on Symptoms and Quality of Life in Coeliac Disease. A Randomized Study** **Reference ID: 733**
Study type	RCT (randomization was carried out using random-number tables)
Study quality	Low quality
Number of patients	Total = 39; GFD with oats = 23, GFD without oats = 16 Withdrawals: GFD with oats = 3, GFD without oats = 0 (reasons for withdrawal: due to gastrointestinal pain and abdominal distension)
Patient characteristics	**Inclusion criteria:** Adult patients with biopsy-proven coeliac disease and all had been on a gluten-free diet without oats, definite, though not necessarily complete, mucosal recovery was evident in all. **Baseline characteristics:** Gender (male/female): GFD with oats = 17/6, GFD without oats = 12/4 Median age (range): GFD with oats = 48 (25-69), GFD without oats = 46 (22-65) Time on GFD (median months, range): GFD with oats = 34 (13-81), GFD without oats = 27 (12-48) The average daily fibre consumption was similar at the time of enrolment, and neither group showed significant alterations in average daily fibre consumption; the average daily consumption of oats in the GFD with oats group was 30g.
Intervention	50g of oats-containing gluten-free products daily
Comparison	To continue their current diet without oats
Length of follow up	12-month
Location	Department of Medicine of Tampere University Hospital, Finland.
Outcomes measures and effect size	Median daily oats consumption in grams (range): At baseline: GFD with oats = 0, GFD without oats = 0 At 12-month: GFD with oats = 28 (0-70), GFD without oats = 0

Bibliographic reference	**Peraaho (2004): Effect of an Oats-Containing Gluten-free Diet on Symptoms and Quality of Life in Coeliac Disease. A Randomized Study** **Reference ID: 733**

Mean Psychological General Well-being questionnaire (PGWB) score (SD):
Baseline: GFD with oats = 103.8 (11.4), GFD without oats = 105.4 (17.2)
At 12-month: GFD with oats = 98.8 (20.0), GFD without oats = 101.3 (16.1); p>0.05

Gastrointestinal symptom rating scale (GSRS):

	GFD with oats (mean, SD)		GDF without oats (mean, SD)		p-values (ANOVA)		
Symptom	Baseline	12-month	Baseline	12-month	Group	Period	Interaction
Total score	1.86 (0.55)	2.00 (0.50)	2.08 (0.77)	1.94 (0.70)	0.917	0.876	0.094
Diarrhoea	1.59 (0.51)	2.03 (0.74)	1.90 (0.88)	1.69 (0.91)	0.645	0.540	***0.010***
Indigestion	2.27 (0.66)	2.06 (0.59)	2.81 (1.17)	2.13 (1.14)	0.597	***0.002***	0.0651
Constipation	1.79 (1.03)	2.24 (0.70)	1.88 (1.22)	2.23 (1.23)	0.785	***0.010***	0.297
Abdominal pain	1.85 (0.73)	1.56 (0.39)	1.85 (0.57)	1.83 (0.58)	0.307	0.267	0.297
Reflux	1.75 (1.07)	2.07 (0.92)	1.63 (1.00)	1.81 (0.87)	0.432	0.051	0.781

Mucosal and laboratory findings (at 12-month):

	GFD with oats (n=18)	GDF without oats (n=13)	p-value
CD3+IELs* αβ+cells γδ+cells	44.6 (22.7) 29.8 (18.8) 11.3 (6.1)	26.7 (21.0) 19.9 (20.3) 5.3 (6.2)	0.039 0.141 0.050
Mean haemoglobin g/L	130	134	>0.05
Mean erythrocyte folate nmol/L	540	489	>0.05
Mean serum iron µmol/L	16.4	17.7	>0.05

*IELs = Intraepithelial lymphocytes/millimetre of epithelium

Bibliographic reference	**Peraaho (2004): Effect of an Oats-Containing Gluten-free Diet on Symptoms and Quality of Life in Coeliac Disease. A Randomized Study** **Reference ID: 733**
Source of funding	This study was supported by the Medical Research Fund of Tampere University Hospital, the Central Hospital of Jyvaskyla and the Yrjo Jahnsson Foundation.
Comments	Randomised using random-number tables, with allocation concealment, blinding (especially assessor) not reported, small sample size, lack of baseline data (e.g. inclusion/exclusion criteria), unclear ITT was carried out.
Author's conclusion: The oats-containing gluten-free diet caused more intestinal symptoms than the traditional diet. Mucosal integrity was not disturbed, but more inflammation was evident in the oats group. Oats provide an alternative in the gluten-free diet, but coeliac patients should be aware of the possible increase in intestinal symptoms.	

Table 4: Benefits and harms of kilned and unkilned oats (adults)

Bibliographic reference	**Kemppainen (2008): Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study** **Reference ID: 437** **Kemppainen (2009): Effect of unkilned and large amounts of oats on nutritional state of celiac patients in remission** **Reference ID: 2595** **Kemppainen (2010): Nutrient intakes during diets including unkilned and large amounts of oats in coeliac disease** **Reference ID: 276** ***Note: multiple publications of the same study.***
Study type	Crossover RCT (only results from first phase before crossover were reported)
Study quality	Low quality
Number of patients	Total = 31; kilned oats = 16, unkilned oats = 15
Patient characteristics	*Inclusion criteria:* Adult patients with coeliac disease 'in remission' who were previously using moderate amounts of regular kilned oats as part of their gluten-free diet. Kilned oats group = 16, Gender (men/women) = 6/10 Unkilned oats group = 15, Gender (men/women) = 7/8 Overall:

Bibliographic reference	**Kemppainen (2008): Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study** **Reference ID: 437** **Kemppainen (2009): Effect of unkilned and large amounts of oats on nutritional state of celiac patients in remission** **Reference ID: 2595** **Kemppainen (2010): Nutrient intakes during diets including unkilned and large amounts of oats in coeliac disease** **Reference ID: 276** ***Note: multiple publications of the same study.***
	• The mean age of the patients (both groups) = 47 (range 16–64) years. • The diagnosis of coeliac disease had been made 8.6 (range 7–29) years earlier. • The patients had followed a gluten-free diet for 8.3 (1–29) years and consumed oats for 5 (0–9) years. • At baseline, 10 patients had partial villous atrophy and 9 had mild mucosal inflammation. Other biopsies were interpreted as normal. In the beginning of the study, all patients had normal (negative) values of EMA antibodies.
Intervention	The goal of the daily intake of oats was 100g. Half of the daily oat portion was given as oat flour and half-baked in oat bread during the 12 months. The daily portion of 100g of oat flour consisted of a minimum of 120 g of oat bread and 50g of oat flour for cooking and baking according to gluten-free oat recipes
Comparison	As above but with unkilned oats. Samples of the oat flours and bread were taken randomly from each process to be tested for purity.
Length of follow up	6-month treatment period (the 12-month follow-up data was not fully reported).
Location	Summer–autumn of 1998 in Kuopio University Hospital area, Finland.
Outcomes measures and effect size	• The consumption increased during the first 6 months from 24 g to 93–96 g daily in both groups (p = 0.01). • The groups using either kilned or unkilned oats did not differ from each other during the follow-up in consumption of oats [Oats in gram, mean (SD): Baseline: Kilned group = 24 (24), Unkilned group = 24 (18); at 6-month: Kilned group = 93 (28), Unkilned = 96 (38); p = 0.74]. • There was no significant change in the histological status of the small intestinal architecture and no abnormal values of EMA occurred during the follow-up (actual measurements not reported). • At 12 months only 5 patients had partial villous atrophy and 4 had mild inflammation (denominator not reported).

Bibliographic reference	**Kemppainen (2008): Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study** **Reference ID: 437** **Kemppainen (2009): Effect of unkilned and large amounts of oats on nutritional state of celiac patients in remission** **Reference ID: 2595** **Kemppainen (2010): Nutrient intakes during diets including unkilned and large amounts of oats in coeliac disease** **Reference ID: 276** ***Note: multiple publications of the same study.***

- At 12-month follow-up no statistically significant changes were found in symptoms, as assessed by verbal rating (actual measurements not reported).
- The group using kilned or unkilned oats did not differ from each other regarding changes in symptoms, including abdominal pain, flatulence and diarrheoa, or welfare during the first 6 months (Mann–Whitney U-test, $p > 0.05$) (categorical data see below Table 1).

Table 1:

	Baseline		At 6-month	
Symptoms	Kilned oats group (n=16)	Unkilned oats group (n=15)	Kilned oats group (n=16)	Unkilned oats group (n=15)
Abdominal pain				
1.Not at all	14	9	11	11
2.To some extent	2	6	5	4
3.Moderate	0	0	0	0
4.Extreme	0	0	0	0
Flatulence				
1.Not at all	6	6	7	6
2.To some extent	9	7	6	6
3.Moderate	1	2	3	2
4.Extreme	0	0	0	0
Abdominal distention				
1.Not at all	13	9	10	11

Bibliographic reference	**Kemppainen (2008): Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study** **Reference ID: 437** **Kemppainen (2009): Effect of unkilned and large amounts of oats on nutritional state of celiac patients in remission** **Reference ID: 2595** **Kemppainen (2010): Nutrient intakes during diets including unkilned and large amounts of oats in coeliac disease** **Reference ID: 276** ***Note: multiple publications of the same study.***

2.To some extent	2	5	4	3
3.Moderate	1	1	2	1
4.Extreme	0	0	0	0
Diarrhoea				
1.Not at all	16	12	12	13
2.To some extent	0	3	3	2
3.Moderate	0	0	1	0
4.Extreme	0	0	0	0

Note: No significant difference between the groups during the first 6 months (Mann-Whitney U-test).

Nine of 31 patients reported abdominal distention. All of them had coeliac disease in remission

	Kilned oats group		Unkilned oats group		p-value*
	Baseline	6-month	Baseline	6-month	
BMI (kg/m2) (mean, SD)					
Men	24 (3)	24 (3)	25 (4)	24 (3)	0.95
Women	25 (3)	25 (3)	23 (3)	23 (3)	0.15
Erythrocyte folate (mean, SD)	490 (159)	582 (185)	430 (87)	496 (102)	0.18
Serum vitamin B-12 (mean, SD)	447 (182)	279 (109)	424 (64)	287 (93)	0.68
Serum calcium (mean, SD)	2.35 (0.11)	2.30 (0.14)	2.40 (0.09)	2.30 (0.10)	0.63
Note: Normal values for the general population: Erythrocyte folate: 315-850nmol/L; Serum vitamin B-12: 140-540pmol/L; Serum calcium: 2.2-2.65mmol/L					

Bibliographic reference	**Kemppainen (2008): Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study** **Reference ID: 437** **Kemppainen (2009): Effect of unkilned and large amounts of oats on nutritional state of celiac patients in remission** **Reference ID: 2595** **Kemppainen (2010): Nutrient intakes during diets including unkilned and large amounts of oats in coeliac disease** **Reference ID: 276** ***Note: multiple publications of the same study.***
	Note: *Difference between groups at 6-month. **Intake of nutrients at 6-month:** *Folic acid in µg, mean (SD):* Baseline: Kilned group = 231 (69), Unkilned group = 214 (99); at 6-month: Kilned group = 235 (79), Unkilned = 226 (64); p = 0.89 *Calcium in mg, mean (SD):* Baseline: Kilned group = 1272 (513), Unkilned group = 1241 (576); at 6-month: Kilned group = 1313 (473), Unkilned = 1213 (692); p = 0.55 *Iron in mg, mean (SD):* Baseline: Kilned group = 12 (3), Unkilned group = 14 (6); at 6-month: Kilned group = 13 (3), Unkilned = 14 (5); p = 0.80
Source of funding	Finnish Cultural Foundation, Antti and Jenny Wihuri Foundation and EVO funding.
Comments	• Methods of randomisation not reported, allocation concealment unclear, blinding unclear. • Potential reporting bias on some outcomes where there was a lack of details. • Only data from the first phase (before crossover) was used, as there was no analysis of crossover effects.
Author's conclusion: Unkilned or kilned oats, even in large amounts produced no harm to the nutritional status of celiac patients during over a 1-year period.	

Bibliographic reference	Gatti (2014) Oats in the diet of children with celiac disease: preliminary results of a double-blind, randomized placebo-controlled multicentre Italian study
Study type	RCT; cross-over trial- only first phase presented here
Study quality	
Number of patients	N=171; Group A = 75, Group B = 96
Patient characteristics	*Inclusion criteria:* • Children aged between 4 - 14 years • Biopsy-proven diagnosis of CD • On a GFD at least 2 years Exclusion criteria: Patients who: • Have another chronic condition i.e. T1D of inflammatory bowel disease • Did not adhere to a GFD • Were on a GFD for less than 2 years
Intervention	Participants were randomised to follow one of 2 diets: A-B treatment • 6 months of diet A, 3 months of standard GFD, 6 months of diet B B-A treatment • 6 months of diet B, 3 months of standard GFD, 6 months of diet A A and B diets consisted of gluten-free products (i.e. pasta, biscuits, cakes, crisps) with either purified oats, or placebo
Comparison	• Clinical data and intestinal permeability tests were measured throughout the study period
Length of follow up	Clinical data measured at 0, 3, 6, 9, 12, and 15 months - This paper looks at preliminary first 6 month results
Location	Italy
Outcomes measures and effect size	306 children were enrolled in the study (mean age 9.62 years) 55/154 and 42/152 patients from group A-B and B-A respectively dropped out within first 6 months (not significant, p=0.14)

Bibliographic reference	Gatti (2014) Oats in the diet of children with celiac disease: preliminary results of a double-blind, randomized placebo-controlled multicentre Italian study
	GSRS score • Group A baseline = 3 (0 - 5.25) • Group B baseline = 2 (0-4.5) • Group A 6 months = 1 (0 - 4.5) • Group B 6 months 0 (0-2) In both groups, a significant reduction in GSRS was seen. There ws no difference between groups in GSRS score
Source of funding	Sponsored by Heinz Italia S.p.A
Comments	• Methods of randomisation not reported, allocation concealment unclear, blinding unclear. • Potential reporting bias on some outcomes where there was a lack of details. • Only data from the first phase (before crossover) was used, as there was no analysis of crossover effects.
Author's conclusion: Oats varieties used for producing the gluten-uncontaminated products used in this study are safe when administered for a 6 month period of time in children with Coeliac disease.	