Table 1: Inclusion/exclusion criteria by level of screening

Objective	Level	Inclusion	Exclusion
Celiac 1	1	Any article reporting sensitivity/specificity of AGA, EMA, tTG, HLA DQ2/DQ8, or biopsy.	Clearly unrelated citation.
	2	For serology and HLA – articles where sensitivity and specificity could be extracted. For biopsy – articles were included if some measure of diagnostic utility could be obtained.	
	3	Articles that allowed determination of sensitivity or specificity for all tests were included.	• Articles with major methodological flaws excluded • Control group did not have gold standard test (biopsy) applied • No description of biopsy criteria given • Celiac group known to be positive for test under evaluation • Control group known to be negative for the test under evaluation • Control groups included patients with Marsh I or II biopsy lesions • AGA test performed without commercial ELISA kit or before 1990
Celiac 2	1	Any potential citation of prevalence or incidence of CD in general and high-risk populations or association of CD with other disorders	Clearly unrelated citation.
	2	Citations limited to those that gave evidence of the prevalence or incidence of CD in the general population or the AHRQ identified high-risk populations (e.g., diabetes, relatives, iron deficiency, osteoporosis). Countries: North America, western Europe, Australia, New Zealand.	Any studies of other CD-associated disorders not identified by the task order. Citations of the prevalence of specific disorders in patients with celiac (i.e., reverse of the inclusion). Any other country.
	3	Incidence and/or prevalence could be extracted from the article.	Serious methodological flaws: • patients identified by surveys, through solicitation of celiac societies • incidence studies without a population density denominator

Table 1 (cont'd): Inclusion/exclusion criteria by level of screening

Objective	Level	Inclusion	Exclusion
Celiac 3	1	Any potential citation of the association, prevalence or risk of lymphoma in CD, including articles on outcome of refractory sprue and ulcerative jejunoileitis.	Clearly unrelated citation.
	2	Measure of risk or prevalence/incidence of lymphoma in a population with CD.	Prevalence of CD in a population of lymphoma. Case reports and non-comparative case series.
	3	Extractable prevalence, incidence, or cumulative risk of lymphoma in CD.	Clonality of lymphocytes in ulcerative jejunoileitis-ileitis not determined or stated (as per TEP). Serious methodological flaw.
Celiac 4	1	Any potential citation of possible consequences of testing for CD.	Clearly unrelated citation.
	2	Consequences extractable from article.	
	3	Consequences limited to the AHRQ list.	Consequences obtainable from the other celiac objective sub-review – i.e., false positive and negative results, etc.
Celiac 5	1	Any potential citation of interventions for the monitoring or promotion of adherence.	Clearly unrelated citation.
	2	Studies of monitoring adherence were included if they assessed monitoring, by biopsy, serology (AGA publication date 1990 or later, EMA, tTG), or both. Any promotion intervention.	Serology prior to 1990.
	3	Data from article could be extracted. Data included follow-up by biopsy alone or serology with biopsy confirmation.	Articles assessing adherence through the measures of intestinal permeability. Studies that reported changes in mean serological titers with a GFD or gluten challenge, but did not address the potential usefulness of a serologic test to assess compliance.

Important articles answering a stated objective but not meeting inclusion criteria (i.e., containing potential threats to internal validity), were presented and discussed in the discussion section.

Data Abstraction

For each objective, a detailed and standardized data abstraction form was developed with the assistance of content experts and the TEP panel. The data abstraction forms included baseline study characteristics as well as questions allowing for the abstraction of all relevant study results and characteristics. The electronic data extraction forms began with basic study and patient

Table 2: Included studies for IgA-AGA in children

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Picarelli, 2000; Italy	Case-control	ESPGAN	22.2*	66.7*	50*	36.3*	0.60*
Gaetano, 1997; Italy	Case-control	ESPGAN	92	68	85.2	80.9	0.67
Carroccio, 1993; Italy	Case-control	Biopsies confirmed at diagnosis, on GFD, and rechallenge (severity grade - not reported)	68	91.7	86.1	79.7	0.43
Hansson, 2000; Sweden	Case-control	ESPGAN	95.5	73.9	77.8	94.4	0.49
Berger, 1996; Switzerland	Case-control	ESPGAN revised with complete villous atrophy	76	67	74	59	0.55
Lerner, 1994; USA, Israel	Case-control	Criteria of Townley modified by Ingkaran	52	94	87	74	0.52
Bahia, 2001; Brazil	Relevant clinical population	Severe villous atrophy	95.5	95.6	91.3	97.9	0.31
Russo, 1999; Canada	Relevant clinical population	ESPGAN	83.3	84.5	64.5	93.8	0.25
Bode, 1993; Denmark	Relevant clinical population	ESPGAN	64	99	90	97	0.07
Poddar, 2002; India	Relevant clinical population	ESPGAN (villous atrophy and unequivocal response to GFD)	94	91.5	92	93.5	0.52
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN	100	94.4	95.7	100	0.55
Lindberg, 1985; Sweden	Relevant clinical population	ESPGAN; Alexander grading	88	88			0.31
Altuntas, 1998; Turkey	Relevant clinical population	Subtotal or total villous atrophy, crypt hyperplasia, increased IEL	23	90	75	48	0.55
Artan, 1998; Turkey	Relevant clinical population	ESPGAN ;	58	51	42.4	66.7	0.38
Rich, 1990; USA	Relevant clinical population	Not recorded - state "severe" lesion	53	93	72.7	85.7	0.25
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected CD)	ESPGAN no details on biopsy findings	95	92.4	76	98.6	0.20
Wolters, 2002; Netherlands	Relevant clinical population (identified retrospectively)	Subtotal villous atrophy with crypt hyperplasia	83	86	81	81	0.51
Lindquist, 1993; Sweden	Relevant clinical population (suspected celiac)	ESPGAN; subtotal or partial villous atrophy	86.5	92.7	93.7	85	0.55
Chirdo, 1999; Argentina	Relevant clinical trial	Total or subtotal villous atrophy	75	87.1	84	80	0.47
Chartrand, 1997; Canada	Relevant clinical population	ESPGAN - with flat mucosal biopsy	80	92	67	96	0.17
Meini, 1996; Italy	Relevant clinical population	Partial villous atrophy or total villous atrophy	0	100	0	91.7	0.08
*30 IgA-EMA-negative patients suspected of CD; 9 of 18 CD patients IgA deficient							

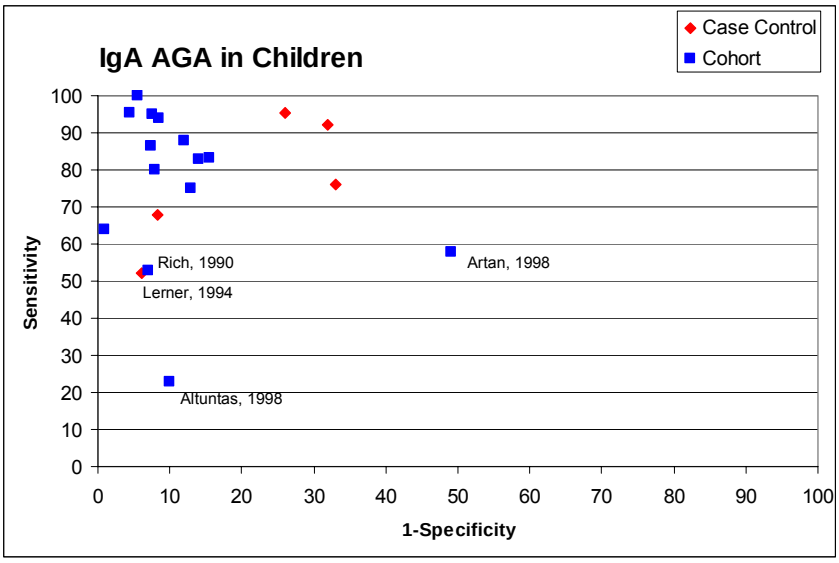
Table 3: Included studies for IgA-AGA in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Sategana-Guidetti, 1995; Italy	Case-control	Roy-Choudhury criteria; partial or total villous atrophy	55	100	100	55.9	35.0
Dahele, 2001; Scotland	Case-control	Included 6 with IEL, rest partial villous atrophy or greater	61	86	88.5	42.7	43.6
Bode, 1994; Denmark	Relevant clinical population	Crypt hyperplasia, villous atrophy and increase inflammatory cells	46	98	75	92	25.7
Kaukinen, 2000; Finland	Relevant clinical population	Villous height to crypt ratio <2.0; IEL and HLA also tested	83	45	75	92	57.0
Maki, 1991; Finland	Relevant clinical population	Severe pathology with crypt hyperplasia to total villous atrophy; mild changes considered normal	30.8	87.2	22.2	91.3	14.8
McMillan, 1991; Ireland	Relevant clinical population	Revised ESPGAN	100	100	100	100	31.5
Bardella, 2001; Italy	Relevant clinical population	Marsh; no grade reported	95	89	76	98	33.3
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected CD)	ESPGAN no details on biopsy findings	92	88.2	85.2	93.8	45.8
Valdimarsson, 1996; Sweden	Relevant clinical population+ a few dypeptic controls	Alexander's classification; partial or subtotal villous atrophy	79	70	28	96	36.8
Vogelsang, 1995; Austria	Relevant study population	Modified ESPGAN; flat mucosa; crypt hyperplasia raised IELs	81.6	83	81.6	83	48.0

Table 4: Included studies for IgA-AGA in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Cataldo, 2000; Italy	Case-control	Original & revised criteria?	20 IgA-deficient CD vs healthy IgA-deficient non-CD	0	100	0	33.3	0.7
Sulkanen, 1998; Finland	Case-control	ESPGAN		84.5	81.6	75.2	89	0.4
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN		90.9	98.5	98	92.7	0.5
Carroccio, 2002; Italy	Relevant clinical population	Marsh, broken down by criteria; CD was diagnosed as enlarged crypts and/or villous atrophy-with normalization on GFD		67	90	86	75	0.5
Tesei, 2003; Argentina	Relevant clinical population	Marsh II to IV - with confirmation		64	92	92	64	0.6

Figure 2: IgA-AGA in children with CD



In contrast, among the 17 analyzed studies (non-IgA deficient) of IgG-AGA conducted in children,[26,27,29,31,34,36,38,42,43,50,52,58,59,68,69,83,85] there seemed to be greater variability in the specificity than in the sensitivity (Table 6; Figure 6). Fifteen of the 17 studies demonstrated sensitivities that were greater than 80%, and six demonstrated sensitivities greater than 90%. Only two studies showed a sensitivity of less than 80%. In contrast, with regards to specificity, two groupings of studies become apparent. The first group consists of 11 studies, all of which had specificities greater than 79%, and except for one study, had sensitivities that were greater than 80%. In contrast, the second group of six studies all had specificities below 70%, and with the exception of one study, had sensitivities greater than 80%. (Tables and figures)

Four studies looked at IgG-AGA in a non-IgA-deficient mixed population of adults and children.[27,37,74,75] Two of these demonstrated sensitivities greater than 80%, one showed a sensitivity of 84%, whereas the second had a sensitivity of 96%. However, only the first study had specificity greater than 80%. In total, three of the four studies had specificities less than 80% (Table 7; Figure 7).

Table 5: Included studies for IgG-AGA in adults

Author, year, country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Sategana-Guidetti, 1995; Italy	Case-control	Roy-Choudhury criteria; partial or total villous atrophy	78	80.7	87.6	67.6	56.7
Bode, 1994; Denmark	Relevant clinical population	Crypt hyperplasia, villous atrophy and increase inflammatory cells	62	97	73	94	34.8
Kaukinen, 2000; Finland	Relevant clinical population	Villous height to crypt ration <2.0; IEL and HLA also tested	17	86	14	93.5	15.1
Maki, 1991; Finland	Relevant clinical population	Severe pathology with crypt hyperplasia to total villous atrophy; mild changes considered normal	46.2	89	33.3	93.3	14.8
McMillan, 1991; Ireland	Relevant clinical population	Revised ESPGAN	57	85	64	81	28.1
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected CD)	ESPGAN no details on biopsy findings	100	69.7	69.4	100	61.0
Vogelsang, 1995; Austria	Relevant study population	Modified ESPGAN; flat mucosa; crypt hyperplasia raised IELs	73.5	73.6	72	75	49.0

Table 6: Included studies for IgG-AGA in children

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Picarelli, 2000; Italy	Case-control	ESPGAN	33.3	58.3	54.5	36.8	0.60
Gaetano, 1997; Italy	Case-control	ESPGAN	100	36	75.7	100	0.67
Carroccio, 1993; Italy	Case-control	Biopsies confirmed at diagnosis, on GFD, and rechallenge (severity grade – not recorded)	88.9	46.7	55.6	84.8	0.43
Hansson, 2000; Sweden	Case-control	ESPGAN	81.8	82.6	81.8	82.6	0.49
Berger, 1996; Switzerland	Case-control	ESPGAN revised with complete villous atrophy	69	59	68	53	0.55
Lerner, 1994; U.S.A, Israel	Case-control	Criteria of Townley modified by Ingkaran	88	92	88	92	0.52
Bahia, 2001; Brazil	Relevant clinical population	Severe villous atrophy	90.9	97.8	95.2	95.7	0.32
Russo, 1999; Canada	Relevant clinical population	ESPGAN	83.3	85.9	66.7	93.8	0.25
Bode, 1993; Denmark	Relevant clinical population	ESPGAN	71	99	100	98	0.07
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN	100	66.7	75.6	100	0.55
Lindberg, 1985; Sweden	Relevant clinical population	ESPGAN; Alexander or Perea et al.	93	89	93.1	88.6	0.31
Altuntas, 1998; Turkey	Relevant clinical population	Subtotal or total villous atrophy, crypt hyperplasia, increased IEL	100	0	55	0	0.55
Artan, 1998; Turkey	Relevant clinical population	ESPGAN	83	59	55.6	85.2	0.38
Rich, 1990; USA	Relevant clinical population	Not reported - state "severe" lesion	100	58	44	100	0.25
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected CD)	ESPGAN no details on biopsy findings	100	92.4	76.9	100	0.20
Wolters, 2002; Netherlands	Relevant clinical population (identified retrospectively)	Subtotal villous atrophy with crypt hyperplasia	83	80	86	82	0.51
Chirdo, 1999; Argentina	Relevant clinical trial	Total or subtotal villous atrophy	85.7	80.6	80	86	0.47
Chartrand, 1997; Canada	Relevant clinical population	ESPGAN - with flat mucosal biopsy	83	79	45	96	0.17
Meini, 1996; Italy	Relevant clinical population	Partial villous atrophy or total villous atrophy	100	80	31.2	100	0.08

Table 7: Included studies for IgG-AGA in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Cataldo, 2000; Italy	Case-control	Original and revised criteria?	20 IgA-deficient CD vs healthy IgA-deficient non-CD	100	100	100	100	0.7
Sulkanen, 1998; Finland	Case-control	ESPGAN		69	73.4	63	78.3	0.4
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN		96.4	69.2	72.6	95.7	0.5
Carroccio, 2002; Italy	Relevant clinical population	Marsh-broke down by criteria; CD was diagnosed as enlarged crypts and/or villous atrophy - with normalization on GFD		76	75	73.4	77.3	0.5
Tesei, 2003; Argentina	Relevant clinical population	Marsh II to IV - with confirmation		84	86	89	79	0.6

Figure 5: IgG-AGA in adults with CD

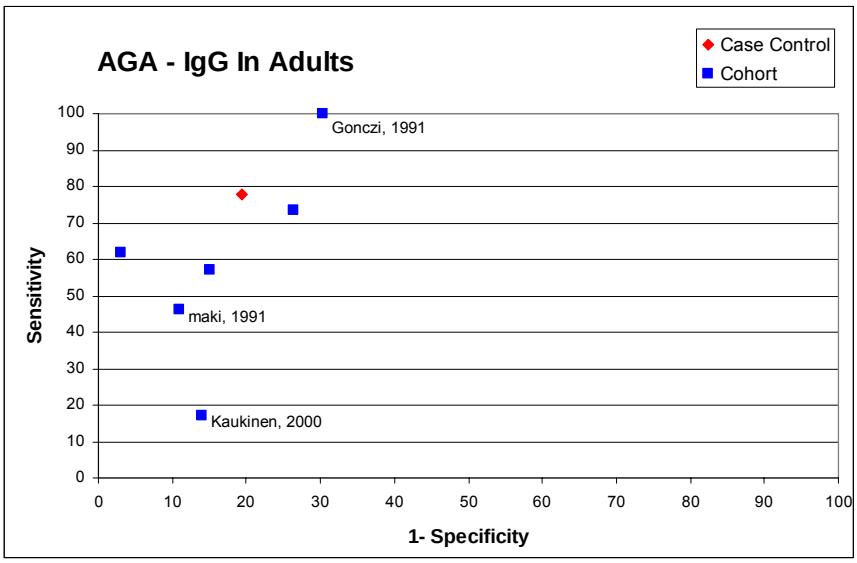


Table 8: Included studies for IgA-EMA-ME in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Hallstrom, 1989; Finland	Case-control	Flat mucosa	90.6	100	100	88.9	51.8
Biagi, 2001; Italy	Case-control	Partial villous atrophy or greater	94.6	100	100	94.5	49.1
Ladinser, 1994; Italy	Case-control	Revised ESPGAN	100	100.0	100	100	21.1
Sategana-Guidetti, 1995; Italy	Case-control	Roy-Choudhury criteria; partial or total villous atrophy	100	100	100	100	63.7
Valentini, 1994; Italy	Case-control	Partial villous atrophy or greater	99	100	100	96.7	76.2
Volta, 1995; Italy	Case-control	Roy-Choudhury criteria	95	100	100	97.1	35.6
Carroccio, 2002; Italy	Relevant clinical population	Ferguson and Murray; partial or total villous atrophy	100	100	100	100	11.6
McMillan, 1991; Ireland	Relevant clinical population	Revised ESPGAN	89.2	100	100	95.3	28.1
Bardella, 2001; Italy	Relevant clinical population	Marsh	100	97.2	93	100	28.7
Valdimarsson, 1996; Sweden	Relevant clinical population+ a few dypeptic controls	Alexander's classification; partial or subtotal villous atrophy	74	100	100	96	9.7
Vogelsang, 1995; Austria	Relevant study population	Modified ESPGAN; flat mucosa; crypt hyperplasia raised IELs	100	100	100	100	48.0

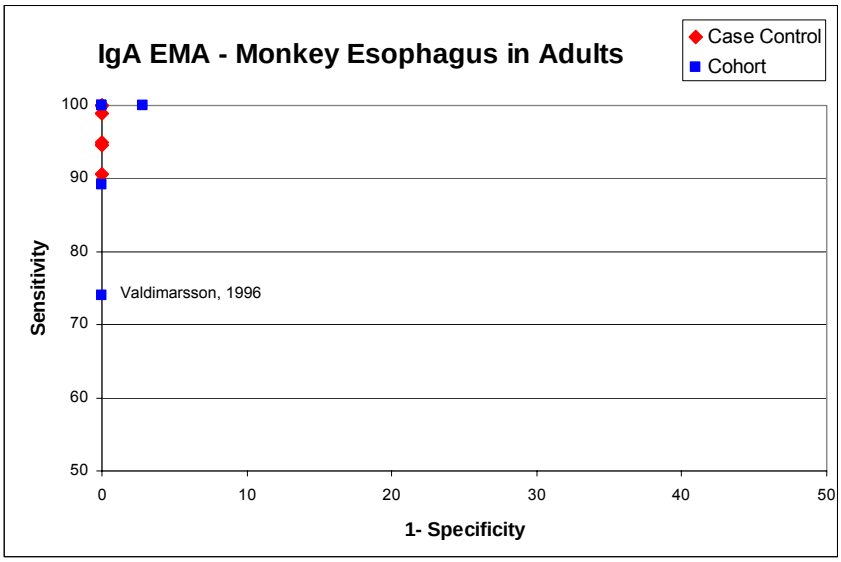
Table 9: Included studies for IgA-EMA-ME in children

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Chirdo, 2000; Argentina	Case-control	ESPGAN	92.4	100	100	85.2	0.7
Kolho, 1997; Finland	Case-control	Revised ESPGAN	95	100	100	97	0.3
Kolho, 1997; Finland	Case-control	Revised ESPGAN	100	100	100	100	0.5
Whelan, 1996; Ireland	Case-control	Subtotal villous atrophy	100	100	100	100	0.4
Bonamico, 2001; Italy	Case-control	ESPGAN	95.1	98.2	90	44.3	0.5
Gaetano, 1997; Italy	Case-control	ESPGAN	96	96	97.9	92.3	0.7
Carroccio, 1993; Italy	Case-control	Biopsies confirmed at diagnosis, on GFD, and rechallenge (severity grade - not reported)	100	96.7	95.7	100	0.4
Di Leo, 2003; Italy	Case-control	ESPGAN	100	96.5	93.5	100	0.4
Vitoria, 2001; Italy	Case-control	Subtotal villous atrophy	100	100	100	100	0.6
Hansson, 2000; Sweden	Case-control	ESPGAN	95.5	100	100	95.8	0.5
Lerner, 1994; USA, Israel	Case-control	Criteria of Townley modified by Ingkaran	97	98	97	98	0.5
Hallstrom, 1989; Finland	Case-control	Flat mucosa	100	100	100	100	0.4
Chan, 2001; Canada	Relevant clinical population	Villous atrophy, crypt hyperplasia, increased lymphocytes	89	97	80	98	0.1
Russo, 1999; Canada	Relevant clinical population	ESPGAN	75	88.7	69.2	91.3	0.3
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN	95.4	100	100	94.7	0.6
Wolters, 2002; Netherlands	Relevant clinical population (identified retrospectively)	Subtotal villous atrophy with crypt hyperplasia	92	90	90.5	92	0.5
Lindquist,1993; Sweden	Relevant clinical population (suspected CD)	ESPGAN; subtotal or partial villous atrophy	98.1	92.7	94.4	97.5	0.6
Kumar, 1989; USA, Israel	Relevant clinical population and control cases	ESPGAN + Townley	96.0	89.0	87.0	96.7	0.2

Table 10: Included studies for IgA-EMA-ME in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Cataldo, 2000; Italy	Case-control	Original & revised criteria?	20 IgA-deficient CD vs healthy IgA-deficient non-CD	0	100	0	33.3	0.7
Dickey, 2001; Northern Ireland	Case-control	Villous atrophy		75.3	98.3	98.2	76	0.6
Ascher, 1996; Sweden	Relevant clinical population	ESPGAN		98.2	100	100	98.5	0.5
Carroccio 2002; Italy	Relevant clinical population	Marsh - broke down by criteria; CD was diagnosed as enlarged crypts and/or villous atrophy - with normalization on a GFD		88	99	98.7	90	0.5
Tesei, 2003; Argentina	Relevant clinical population	Marsh II to IV - with confirmation		86	100	100	83	0.6

Figure 8: IgA-EMA-ME in adults with CD



found to be IgA deficient. In this highly selected population, the reported sensitivity and specificity of IgG-EMA-ME were both 100%.

Table 11: Included studies for IgG-EMA-ME in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
McMillan, 1991; Ireland	Relevant clinical population	Revised ESPGAN	39	98.3	92	78	13.5

Table 12: Included studies for IgG-EMA-ME in children

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Picarelli, 2000; Italy	Case-control	ESPGAN	30 IgA-EMA neg. pts suspected of CD; 9/18 CD patients IgA deficient	100	100	100	100	0.1

EMA—HU. IgA-EMA-HU was assessed in 13 studies. Six of these studies were conducted in adults,[45,49,54,57,61,70,89] five in children,[36,53,55,69,70] and two in a mixed population.[72,74] One study provided summary statistics without the raw two-by-two table results,[69] however the raw data was calculated from the reported sensitivity and specificity and the group numbers. One study provided data on two different populations (including different control groups).[55]

IgG-EMA-HU was not assessed in any of the studies meeting our inclusion criteria.

Two studies included CD patients (both adult and children) with less than a Marsh IIIa grade, and reported IgA-EMA-HU sensitivities of 87% and 100%.[45]
[70]

IgA-EMA-HU. Six studies in adults assessed IgA-EMA-HU (Table 13; Figure 11).[45,49,54,57,61,70,89] In all six, the specificity was reported to be 100%. There was, however, variability in the reported sensitivities, which ranged from 87% to 100%. Three studies demonstrated sensitivities between 87% and 89%, two between 90% and 95% and one showing a sensitivity of 100%. There was no observed statistical heterogeneity for this analysis. The pooled sensitivity and specificity was found to be 90.2% (95% CI: 85.9-93.4) and 100% (95% CI: 99.1-100), respectively.

Five studies with six separate child populations assessed IgA-EMA-HU (Table 14; Figure 12).[36,53,55,69,70] Four of the six studies were grouped together and revealed sensitivities between 94% and 100%, and specificities of 100%. Of the two outliers,[90] one showed a sensitivity of 100% and a specificity of 77%. The other study,[69] was an outlier in other analyses, and demonstrated a sensitivity of 46% and a specificity of 96%. The authors comment on difficulties of interpretation of the immunofluorescence as a likely explanation. After accounting for this study, there was no statistical heterogeneity documented for sensitivity. The pooled sensitivity for this analysis was 96.9% (95% CI: 93.5-98.6). A pooled specificity for this analysis was not calculated, but is likely close to 100% given that four of the five grouped studies demonstrated a specificity of 100%.

Two studies assessed IgA-EMA-HU in a mixed-age population (Table 15; Figure 13).[72,74] In both these studies, the specificity was 100% (95% CI: 97.5-100) and the sensitivity 93% (95% CI: 88.1-95.4).

Table 13: Included studies for IgA-EMA-HU in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Gillbert, 2000; Canada	Case-control	Mild, moderate, severe villous atrophy	100	100	100	100	33.3
Ladinser, 1994; Italy	Case-control	Revised ESPGAN	90	100	100	98	18.9
Salmaso, 2001; Italy	Case-control	Grades I-IV Marsh with response to a GFD	87	100	100	95.1	24.7
Volta, 1995; Italy	Case-control	Roy-Choudhury criteria	95	100	100	97.1	35.6
Dahele, 2001; Scotland	Case-control	Included 6 with IEL, rest partial villous atrophy or greater	87	100	100	81.3	55.3
Kaukinen, 2000; Finland	Relevant clinical population	Villous height to crypt ration <2.0; IEL and HLA also tested	88.9	100	100	98.9	7.6

Table 14: Included studies for IgA-EMA-HU in children

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Kolho, 1997; Finland	Case-control	Revised ESPGAN	95	100	100	97	0.3
Kolho, 1997; Finland	Case-control	Revised ESPGAN	100	100	100	100	0.5
Gaetano, 1997; Italy	Case-control	ESPGAN	94	100	100	89.2	0.7
Salmaso, 2001; Italy	Case-control	Grades I-IV Marsh with response to GFD	100	100	100	100	0.6
Russo, 1999; Canada	Relevant clinical population	ESPGAN	45.8	95.8	78.6	84	0.3
Iltanen, 1999 Finland	Relevant clinical population	ESPGAN - CD confirmed at follow-up	100	77.1	60.1	100	0.3

Table 15: Included studies for IgA-EMA-HU in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Sblaterro, 2000; Italy	Case-control	ESPGAN	93	100	100	80	0.8
Sulkanen, 1998; Finland	Case-control	ESPGAN	92.6	99.5	99.2	94.9	0.4

Figure 11: IgA-EMA-HU in adults with CD

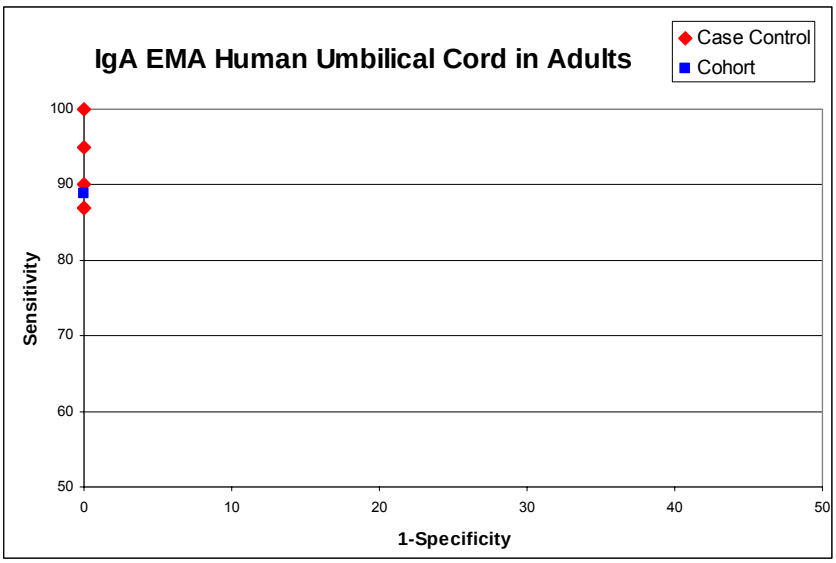


Table 16: Included studies for IgA-tTG-GP in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Biagi, 2001; Italy	Case-control	Partial villous atrophy or greater	87.5	98.1	98	87.1	46.3
Salmaso, 2001; Italy	Case-control	Grades I-IV Marsh with response to a GFD	87	97	90.9	94.9	27.2
Dahele, 2001; Scotland	Case-control	Included 6 with IEL, rest partial villous atrophy or greater	81	97	97.9	74.1	52.5
Carroccio, 2002; Italy	Relevant clinical population	Ferguson and Murray; partial or total villous atrophy	100	92	60	100	18.8
Bardella, 2001; Italy	Relevant clinical population	Marsh	100	98.2	83.3	100	10.0

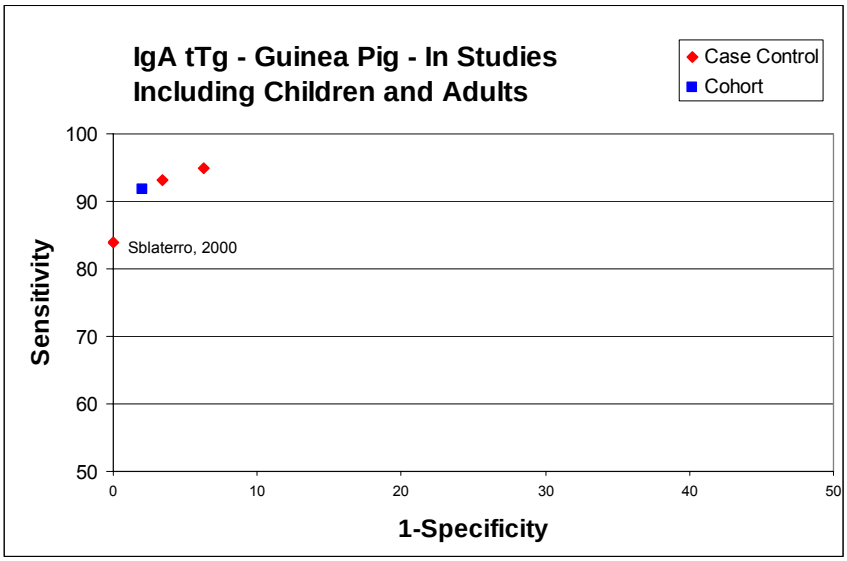
Table 17: Included studies for IgA-tTG-GP in children

Author, country; year	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Bonamico, 2001; Italy	Case-control	ESPGAN	90.3	100	100	30.3	0.5
Salmaso, 2001; Italy	Case-control	Grades I-IV Marsh with response to a GFD	95	100	100	94.1	0.6
Hansson, 2000; Sweden	Case-control	ESPGAN	90.9	95.7	95.2	91.7	0.5
Chan, 2001; Canada	Relevant clinical population	Villous atrophy, crypt hyperplasia, increase lymphocytes	89	94	67	98	0.1
Wolters, 2002; Netherlands	Relevant clinical population (identified retrospectively)	Subtotal villous atrophy with crypt hyperplasia	96	92	92.6	95.7	0.5

Table 18: Included studies for IgA-tTG-GP in studies including both adults and children

Author, year, country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Dickey, 2001; Northern Ireland	Case-control	Villous atrophy	93.2	96.6	97.1	91.8	0.6
Sblaterro, 2000; Italy	Case-control	ESPGAN	84	100	100	62.5	0.8
Sulkanen, 1998; Finland	Case-control	ESPGAN	95	93.7	90.8	96.5	0.4
Troncone, 1999; Italy	Relevant clinical population	ESPGAN	91.7	98	98	94	0.4

Figure 16: IgA-tTG-GP in adults and children with CD



IgG-tTG-GP. Two studies in a mixed-age population assessed IgG-tTG- GP (Table 19; Figure 17).[72,76] The specificities in both studies were greater than 98%, but the sensitivities were 23% and 62%, respectively.

Table 19: Included studies for IgG-tTG-GP in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Sblaterro, 2000; Italy	Case-control	ESPGAN	61.5	100	100	44.4	0.8
Troncone, 1999; Italy	Relevant clinical population	ESPGAN	23	98	92	63	0.4

Table 20: Included studies for IgG-tTG-HR in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Cataldo, 2000; Italy	Case-control	Original & revised criteria?	20 IgA-deficient CD vs healthy IgA-deficient non-CD	100	80	90.1	100	0.7
Sblaterro, 2000; Italy	Case-control	ESPGAN		67.6	100	100	48.7	0.8

IgA-tTG-HR. Three studies assessed IgA-tTG-HR in an adult population (Table 21; Figure 18).[39,49,54] There was very little variability in the reported values for the sensitivities and specificities. The sensitivities were 100% in two studies, and 95% in the other. The specificities were 100% in two studies, and 97% in another. The pooled estimates of the sensitivity and specificity were 98.1% (95% CI: 90.1%-99.7%) and 98.0% (95% CI: 95.8-99.1), respectively.

Among the three studies in children (Table 22; Figure 19),[52,79,83] the sensitivities were 96% in two studies and 95% in one. The specificities were 100% in two studies, and 96% in one. The pooled estimates of the sensitivity and specificity were 95.7% (95% CI: 90.3-98.1) and 99.0% (95% CI: 94.6-99.8), respectively.

Only two studies assessed the IgA-tTG-HR in a mixed-age population without IgA deficiency (Table 23; Figure 20).[72,75] The sensitivities and specificities were 92% and 100%, respectively, for the first study, and 91% and 96%, respectively, for the second. The pooled estimates of the sensitivity and specificity were 90.2% (95% CI: 86.4-93.0) and 95.4% (95% CI: 91.5- 97.6), respectively.

Overall, these studies demonstrated a specificity of close to 100% and sensitivity in the range of 90% to 96%.

Table 21: Included studies for IgA-tTG-HR in adults

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev (%)
Carroccio, 2002; Italy	Relevant clinical population	Ferguson and Murray; partial or total villous atrophy	100	97	80	100	14.5
Gillbert, 2000; Italy	Case-control	Mild, moderate, severe villous atrophy	95.2	100	95.2	100	31.7
Kaukinen, 2000; Finland	Relevant clinical population	Villous height to crypt ration <2.0; IEL and HLA also tested	100	100	100	100	8.7

Table 22: Included studies for IgA-tTG-HR in children

Author, year; country	Study type	Biopsy criteria	Sens	Spec	PPV	NPV	Prev
Vitoria, 2001; Italy	Case-control	Subtotal villous atrophy	95	100	100	93	0.6
Hansson, 2000; Sweden	Case-control	ESPGAN	95.5	95.7	95.5	95.7	0.5
Wolters, 2002; Netherlands	Relevant clinical population (identified retrospectively)	Subtotal villous atrophy with crypt hyperplasia	96	100	100	96	0.5

Table 23: Included studies for IgA-tTG-HR in studies including both children and adults

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Cataldo, 2000; Italy	Case-control	Original & revised criteria?	20 IgA deficient CD vs healthy IgA-deficient non-CD	0	100	0	33.3	0.7
Sblaterro, 2000; Italy	Case-control	ESPGAN		91.5	100	100	76.9	0.8
Tesei, 2003; Argentina	Relevant clinical population	Marsh II to IV - with confirmation		91	96	97	87	0.6

Figure 18: IgA-tTG-HR in adults with CD

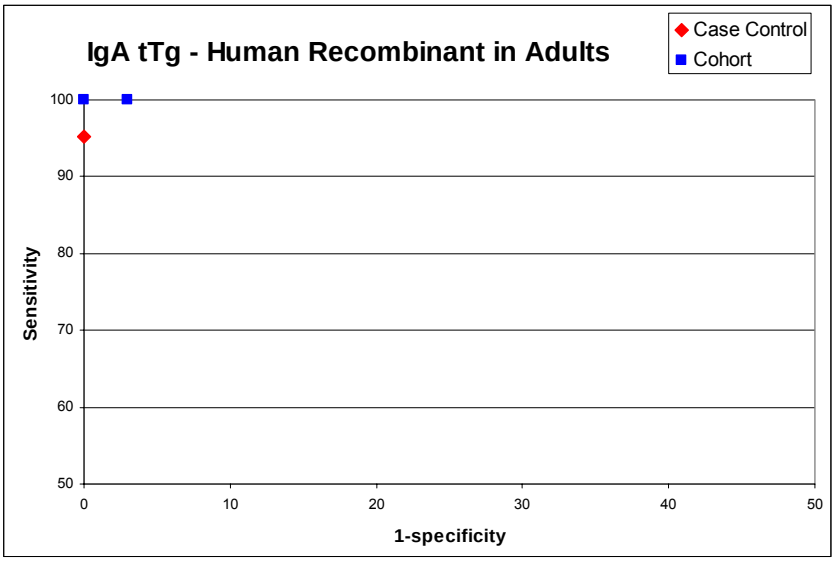


Table 24: Included studies for combination IgA and IgG AGA, when either test is positive

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Valentini, 1994; Italy	Case-control	Partial villous atrophy or greater	Adults	92	90	96.8	77.1	0.76
Bode, 1994; Denmark	Relevant clinical population	Crypt hyperplasia, villous atrophy and increase inflammatory cells	Adults	77	95	71	97	0.41
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected celiac)	ESPGAN no details on biopsy findings	Adults	100	97.1	96.2	100	0.44
Bode, 1993; Denmark	Relevant clinical population	ESPGAN	Children	86	99	92	99	0.1
Falth-Magnusson, 1994; Sweden	Relevant clinical population	ESPGAN + Alexander grading IV, grade III to IV challenge	Children	88.5	93.7	88.8	93.5	0.4
Lindberg, 1985; Sweden	Relevant clinical population	ESPGAN, Alexander grading	Children	97	83	41.8	98.2	0.3
Artan, 1998; Turkey	Relevant clinical population	ESPGAN	Children: IgA AGA or IgG AGA	83	36	44	77.8	0.3
Gonczi, 1991; Australia	Relevant clinical population (184 children with suspected CD)	ESPGAN no details on biopsy findings	Children	100	98.7	95.2	98.7	0.2
Chartrand, 1997; Canada	Relevant clinical population	ESPGAN – with flat mucosal biopsy	Children	93	71	43	98	0.2

Table 25: Included studies for combination IgA and IgG tTG-HR, when either test is positive

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Sblaterro, 2000; Italy	Case-control	ESPGAN	Adults and children	98.5	100	100	95.2	0.8

Table 26: Included studies for combination IgA-AGA and IgG-EMA-HU, when either test is positive

Author, year; country	Study type	Biopsy criteria	Notes	Sens	Spec	PPV	NPV	Prev
Russo, 1999; Canada	Relevant clinical population	ESPGAN	Children	100	73	57	82	0.3

Table 27: Weighted pooled estimates with 95% CIs and heterogeneity identified

Analysis	Sens	L 95% CI:	U 95% CI:	Spec	L 95% CI:	U 95% CI:	Prev	L 95% CI:	U 95% CI:	PPV	L 95% CI:	U 95% CI:	NPV	L 95% CI:	U 95% CI:
IgA-AGA–ADULT	H	H	H	H	H	H	0.358	0.332	0.385	H	H	H	H	H	H
IgG-AGA–ADULT	H	H	H	H	H	H	0.367	0.335	0.401	H	H	H	H	H	H
IgA-EMA-ME–ADULT	0.974	0.957	0.985	0.996	0.988	0.999	0.398	0.371	0.425	0.974	0.957	0.985	0.996	0.988	0.999
IgG-EMA-ME–ADULT (one study)	0.393	0.236	0.576	0.984	0.913	0.997	0.135	0.079	0.221	0.393	0.236	0.576	0.984	0.913	0.997
IgA-EMA-HU–ADULT	0.902	0.859	0.934	1.000	0.991	1.000	0.331	0.297	0.368	0.902	0.859	0.934	1.000	0.991	1.000
IgA-tTG-GP—ADULT	0.859	0.808	0.898	0.953	0.930	0.969	0.312	0.279	0.348	0.859	0.808	0.898	0.953	0.930	0.969
IgA-tTG-HR–ADULT	0.981	0.901	0.997	0.981	0.958	0.991	0.160	0.126	0.202	0.981	0.901	0.997	0.981	0.958	0.991
IgA-AGA–CHILD	H	H	H	H	H	H	0.363	0.341	0.385	H	H	H	H	H	H
IgG-AGA–CHILD	H	H	H	H	H	H	0.437	0.413	0.462	H	H	H	H	H	H
IgA-EMA-ME–CHILD	0.961	0.945	0.973	0.974	0.963	0.982	0.400	0.378	0.423	0.961	0.945	0.973	0.974	0.963	0.982
IgA-EMA-HU–CHILD	0.969	0.935	0.986	H	H	H	0.447	0.402	0.493	0.969	0.935	0.986	0.949	0.915	0.970
IgA-tTG-GP–CHILD	0.931	0.888	0.959	0.963	0.931	0.980	0.446	0.401	0.493	0.931	0.888	0.959	0.963	0.931	0.980
IgA-tTG-HR–CHILD	0.957	0.903	0.981	0.990	0.946	0.998	0.519	0.452	0.584	0.957	0.903	0.981	0.990	0.946	0.998
IgA-AGA–MIXED	H	H	H	H	H	H	0.415	0.386	0.444	H	H	H	H	H	H

H = significant heterogeneity by Pearson's Chi square

Table 27 (cont'd): Weighted pooled estimates with 95% CIs and heterogeneity identified

Analysis	Sens	L 95% CI:	U 95% CI:	Spec	L 95% CI:	U 95% CI:	Prev	L 95% CI:	U 95% CI:	PPV	L 95% CI:	U 95% CI:	NPV	L 95% CI:	U 95% CI:
IgG-AGA–MIXED	H	H	H	H	H	H	0.510	0.480	0.540	H	H	H	H	H	H
IgA-EMA-ME–MIXED	H	H	H	0.995	0.982	0.999	0.467	0.434	0.500	0.859	0.825	0.888	0.995	0.982	0.999
IgA-EMA-HU–MIXED	0.925	0.881	0.954	0.996	0.975	0.999	0.437	0.391	0.484	0.925	0.881	0.954	0.996	0.975	0.999
IgA-tTG-GP–MIXED	H	H	H	0.954	0.927	0.972	0.463	0.425	0.501	0.913	0.877	0.939	0.954	0.927	0.972
IgG-tTG-GP–MIXED	0.451	0.363	0.543	0.988	0.935	0.998	0.265	0.208	0.331	0.451	0.363	0.543	0.988	0.935	0.998
IgA-tTG-HR–MIXED	0.902	0.864	0.930	0.954	0.915	0.976	0.573	0.530	0.616	0.902	0.864	0.930	0.954	0.915	0.976
IgG-tTG-HR–MIXED (one study)	0.677	0.556	0.778	1.000	0.839	1.000	0.518	0.413	0.621	0.677	0.556	0.778	1.000	0.839	1.000

H = significant heterogeneity by Pearson's Chi square
Note: see Appendix G for raw pooled data by antibody test

aspect of this study is presented in its respective section. In this study, HLA DQ2 was found in 19 of 21 (90.5%) of patients with CD as apposed to 29 out of 67 (29.9%) of the control patients. Elevated γδ+ IEL density was significantly associated with DQ2 positivity. The calculated diagnostic measures for this study are presented in Table 28. In this population, DQ2 demonstrated a high sensitivity of 90.5% but a relatively modest specificity of only 70%, which is understandable given that the control population had a fairly high frequency of DQ2 positivity. The prevalence of CD in the study population was 1:4.2 (or 24%). The PPV was 49% and the NPV was 96%, suggesting that a negative DQ2 test result provides the greatest diagnostic information.

Sacchetti et al.[152] studied a group of Italian children suspected of having CD. Patients fulfilling the ESPGAN criteria were classified as having CD (n = 48 of 80), whereas, the remainder (n=32) were considered disease controls. The authors also used a second retrospectively defined group of known CD patients by ESPGAN criteria (n = 74), and a second group control of 180 unbiopsied healthy subjects. HLA DQ2 was determined in the CD group as a whole and in the two control groups, with the results presented in Table 28. In this study, the sensitivity of HLA DQ2 was 88.9% and the specificity was 81% for the comparison with the biopsied controls; the sensitivity of HLA DQ2 was 88.9% and the specificity was 73% for the comparison with the unbiopsied controls. Interestingly, in this study only 18.8% of the biopsy-negative controls were positive for HLA DQ2, whereas, 26.7% of the unbiopsied controls were HLA DQ2 positive. This difference accounts for the higher specificity seen for HLA DQ2 in the comparison with the biopsy-negative control group as compared with the comparison with the healthy controls. The prevalence of CD in the studied population was also quite high in both portions of this study (79% for comparison with biopsied controls and 51% for the comparison with unbiopsied controls). As such the PPV and the NPV of HLA DQ2 in this study were 95% and 62%, respectively. The difference in prevalence between this and the Iltanen study accounts for the differences seen in the PPVs and NPVs.

Table 28: HLA studies with biopsied cases and controls

Author, year; country	Prev of CD	DQ2 in CD	DQ2 in controls	Sensitivity	Specificity	PPV	NPV	CD population
Iltanen, 1999; Finland	0.24	90.48	29.85	90%	70%	49%	96%	Known CD versus biopsied controls
Sacchetti, 1998; Italy	0.79	86.89	18.75	87%	81%	95%	62%	Known CD versus biopsied controls
	0.51	86.89	26.72	87%	73%	77%	84%	Versus unbiopsied healthy controls

Table 29: Prevalence/frequency of HLA DQ2 and HLA DQ8 in prevalence and mixed-design studies, and in case-control studies with HLA DQ8 data

Author	Year	Country	# of CD	% DQ2	% DQ8	% DQ2/8	Population with CD
Lewis	2000	USA	101	90.10	n/a	n/a	Confirmed cases among CD relatives
Book	2001	USA	8	87.50	12.50	100	Down Syndrome
Book	2003	USA	34	n/a	n/a	97.06	Affected 1st-degree relatives of CD sib. pairs
Csizmadia	2000	Netherlands	10	100	20	n/a	Down Syndrome
Fasano	2003	USA	98	83.67	22.45	100	Screened large population only subset tested for HLA
Iltamen	1999	Finland	5	100	n/a	n/a	Sjogren's syndrome
Kaukinen	2000	Finland	6	100	n/a	n/a	Known CD
Maki	2003	Finland	56	85.71	n/a	n/a	Screen of school-age children
Mustalahti	2002	Finland	29	100	n/a	n/a	Relatives of CD or DH
Catassi	2001	Algeria	79	91.3	n/a	95.6	Saharawi Arabs
Lui	2002	Finland	260	96.92	2.69	99.62	Family members of celiacs
Polvi	1996	Finland	45	100	n/a	n/a	Known CD
Ploski / Sollid	1996	Sweden	135	91.85	4.44	96.30	Known CD
Popat	2002	Sweden	62	93.55	n/a	n/a	Known CD
Larizza	2001	Italy	7	100	n/a	n/a	Children with autoimmune thyroid disease, EMA+biopsy
Failla	1996	Italy	7	14.29	n/a	n/a	Down Syndrome (only 7 CD cases)
Farre	1999	Spain	60	93.33	n/a	n/a	1st-degree relatives of celiacs
Balas	1997	Spain	212	94.81	4.25	99.06	Known CD
Zubillaga	2002	Spain	135	92.59	3.70	96.0 (calc)	Mostly CDs, some CD in subjects with Down Syndrome and subjects with diabetes
Karell	2003	France	92	86.96	6.52	93.48	Known CD
		Italy	302	93.71	5.63	89.40	
		Finland	100	91	5.00	96.00	
		Norway/ Sweden	326	91.41	5.21	96.63	
		Uk	188	87.77	7.98	95.74	
		Total	1008	93.71	5.95	93.95	
Kaur	2002	India	35	97.14	n/a	n/a	Known CD
Neuhausen	2002	Israel	23	82.61	56.52	100	Bedouin Arabs
Tuysuz	2001	Turkey	55	83.64	16.36	90.91	Children with known CD
Bouguerra	1996	Tunisia	94	84.04	n/a	n/a	Known CD
Sumnik	2000	Czech	15	80	66.67	100	Diabetics
Perez-Bravo	1999	Chile	62	11.29	25.81	37.10	Chileans

DH = dermatitis herpetiformis

Table 30: Sensitivity/specificity (calculated) for HLA DQ2 in case-control studies

Author, year; country	Prev of CD	% DQ2 in CD	% DQ2 in Controls	Sens	Spec	PPV	NPV	CD population
Fine, 2000; USA	0.06	88 (22/25)	31.24 (134/429)	0.88	0.69	0.14	0.99	Known CD
Howell, 1995; UK	0.38	91.21 (83/91)	23.18 (35/151)	0.91	0.77	0.7	0.94	Known CD
Michalski, 1995; Ireland	0.62	96.67 (87/90)	39.29 (22/56)	0.97	0.61	0.8	0.92	Known CD
Colonna, 1990; Italy	0.36	94.59 (140/148)	40.82 (109/267)	0.95	0.59	0.56	0.95	Known CD
Catassi, 2001; Algeria	0.37	91.1 (72/79)	38.9 (53/136)	0.91	0.61	0.58	0.92	Saharawi Arabs
Congia, 1991; Italy	0.2	96 (24/25)	34 (34/100)	0.96	0.66	0.41	0.99	Known CD
Ferrante, 1992; Italy	0.48	88 (44/50)	16.36 (9/55)	0.88	0.84	0.83	0.88	Known CD
Mazzilli, 1992; Italy	0.5	92 (46/50)	18 (9/50)	0.92	0.82	0.84	0.91	Known CD
Tighe, 1992; Italy	0.49	70.59 (39/43)	8.33 (5/41)	0.91	0.88	0.89	0.9	Known CD
Castro, 1993; Italy	0.38	80 (4/5)	37.5 (3/8)	0.8	0.63	0.57	0.83	Down Syndrome
Lio, 1997; Italy	0.45	100 (18/18)	63.64 (14/22)	1	0.36	0.56	1	Known CD
Sacchetti, 1998; Italy	0.79	86.89 (106/122)	18.75 (6/32)	0.87	0.81	0.95	0.62	Known CD and biopsied controls
Sacchetti, 1998; Italy	0.51	86.89 (106/122)	26.72 (31/116)	0.87	0.73	0.77	0.84	Healthy controls
Iltamen, 1999; Finland	0.24	90.48 (19/21)	29.85 (20/67)	0.9	0.7	0.49	0.96	Known CD
Ploski/Sollid, 1993; Sweden	0.34	94.68 (89/94)	25.97 (47/181)	0.95	0.74	0.65	0.96	Known CD
Pattersson, 1933; Sweden	0.4	92.31 (60/65)	43.75 (42/96)	0.92	0.56	0.59	0.92	Known CD
Ploski/Sollid, 1996; Sweden	0.43	91.85 (124/135)	22.35 (40/179)	0.92	0.78	0.76	0.93	CD vs blood donors
Fernandez-Arquero, 1995; Spain	0.36	92 (92/100)	25.56 (46/180)	0.92	0.74	0.67	0.94	Known CD
Arranz, 1997; Spain	0.5	92 (46/50)	24 (12/50)	0.92	0.76	0.79	0.9	Known CD
Balas, 1997; Spain	0.22	94.81 (201/212)	29.25 (217/742)	0.95	0.71	0.48	0.98	Known CD

Table 30 (cont'd): Sensitivity/specificity (calculated) for HLA DQ2 in case-control studies

Author, year; country	Prev of CD	% DQ2 in CD	% DQ2 in Controls	Sens	Spec	PPV	NPV	CD population
Ruiz Del Prado, 2001; Spain	0.04	94.74 (36/38)	39.22 (351/895)	0.95	0.61	0.09	1	Known CD
Dijilali-Saiah, 1994; France	0.27	88.75 (71/80)	21.13 (45/213)	0.89	0.79	0.61	0.95	Known CD
Dijilali-Saiah, 1998; France	0.44	83.17 (84/101)	20 (26/130)	0.83	0.8	0.76	0.86	Known CD
Tighe, 1993; Israel	0.51	90.7 (24/34)	12.2 (3/36)	0.71	0.92	0.89	0.77	Ashkenazi Jews, known CD
Arnason, 1994; Iceland	0.13	84 (21/25)	36.36 (60/165)	0.84	0.64	0.26	0.96	Known CD
Boy, 1994; Sardinia	0.5	96 (48/50)	32 (16/50)	0.96	0.68	0.75	0.94	Known CD
Congia, 1994; Sardinia	0.42	90.77 (59/65)	39.33 (35/89)	0.91	0.61	0.63	0.9	Known CD
Erkan, 1999; Turkey	0.5	40 (12/30)	6.67 (2/30)	0.4	0.93	0.86	0.61	Known CD
Tumer, 2000; Turkey	0.3	51.52 (17/33)	25.97 (20/77)	0.52	0.74	0.46	0.78	Turkish, known CD
Tuysuz, 2001; Turkey	0.52	83.64 (46/55)	24 (12/50)	0.84	0.76	0.79	0.81	Turkish, known CD
Perez-Bravo, 1999; Chile	0.33	11.29 (7/62)	2.42 (3/124)	0.11	0.98	0.7	0.69	Chilean

Table 31: Sensitivity/specificity (calculated) for HLA DQ2 in mixed-design studies

Author, year; country	Prev of CD	% DQ2 in CD	% DQ2 in controls	Sens	Spec	PPV	NPV	CD population
Book, 2001; USA	0.09	87.50 (7/8)	15.58 (12/77)	0.88	0.84	0.37	0.98	Down Syndrome
Csizmadia, 2000; Netherlands	0.11	100 (10/10)	28 (25/90)	1.00	0.72	0.29	1.00	Down Syndrome
Fasano, 2003; USA	0.52	83.67 (82/98)	42.39 (39/92)	0.84	0.58	0.68	0.77	9019 at risk, 4126 not at risk
Larizza, 2001; Italy	0.08	100 (7/7)	34.62 (27/78)	1	0.65	0.21	1	Children with autoimmune thyroid disease, EMA+biopsy
Polvi, 1996; Finland	0.58	100 (45/45)	28.13 (9/32)	1	0.72	0.83	1	CD vs various controls
Iltamen, 1999; Finland	0.15	100 (5/5)	n/a	1	n/a	n/a	n/a	Sjogren's syndrome
Kaukinen, 2000; Finland	0.17	100 (6/6)	n/a	1	n/a	n/a	n/a	CD vs disease controls
Lui, 2002; Finland	0.52	96.92 (252/260)	57.38 (136/237)	0.97	0.43	0.65	0.93	Family members of celiacs (controls=unaffected family members)
Farre, 1999; Spain	0.55	93.33 (56/60)	18 (9/50)	0.93	0.82	0.86	0.91	CD vs healthy controls
	0.26	93.33(56/60)	63.91(108/169)	0.93	0.36	0.34	0.94	CD vs relatives of CD
Sumnik, 2000; Czech	0.07	80 (12/15)	49.46 (92/186)	0.8	0.51	0.12	0.97	Diabetes (control=EMA neg.)
Kaur, 2002; India	0.11	97.14 (34/35)	4.64 (13/280)	0.97	0.95	0.72	1	CD vs healthy controls
Neuhausen, 2002; Israel	0.31	82.61 (19/23)	61.54 (32/52)	0.83	0.38	0.37	0.83	Bedouin Arabs (some cases and controls not biopsied)

Table 32: Sensitivity/specificity (calculated) for HLA DQ8

Author, year; country	Prev of CD	DQ8 in CD	DQ8 in controls	Sens	Spec	PPV	NPV	CD population
Csizmadia, 2000; Netherlands	0.11	20 (2/10)	20 (18/90)	0.20	0.80	0.10	0.90	Down Syndrome
Fasano, 2003; USA	0.52	22.45 (22/98)	20.65 (19/92)	0.22	0.79	0.54	0.49	Screened at-risk and not-at-risk populations
Lui, 2002; Finland	0.52	2.69 (7/260)	10.55 (25/237)	0.03	0.89	0.22	0.46	Family members of CD patients (controls=unaffected family members)
Ploski/Sollid 1996; Sweden	0.43	4.44 (6/135)	25.14 (45/179)	0.04	0.75	0.12	0.51	Known CD
Balas, 1997; Spain	0.22	4.25 (9/212)	16.85 (125/742)	0.04	0.83	0.07	0.75	Known CD
Sumnik, 2000; Czech	0.07	66.67 (10/15)	65.59 (122/186)	0.67	0.34	0.08	0.93	Diabetes
Neuhausen, 2002; Israel	0.31	56.52 (13/23)	25 (13/52)	0.57	0.75	0.5	0.8	Bedouin Arabs
Tuysuz, 2001; Turkey	0.52	16.36 (9/55)	8 (4/50)	0.16	0.92	0.69	0.5	Turkish known CD
Perez-Bravo, 1999; Chile	0.33	25.81 (16/62)	12.9 (16/124)	0.26	0.87	0.5	0.7	Chileans

Table 33: Sensitivity/specificity (calculated) for HLA DQ2 or DQ8

Author; year; country	Prev of CD	DQ2 or DQ8 in CD	DQ2 or DQ8 in controls	Sens	Spec	PPV	NPV	Notes
Fasano, 2003; USA	0.52	100 (98/98)	59.78 (55/92)	1	0.4	0.64	1	Screened at-risk and not-at-risk populations
Catassi, 2001; Algeria	0.37	96.2 (76/79)	41.9 (57/136)	0.96	0.58	0.57	0.96	Saharawi Arabs
Lui, 2002; Finland	0.52	99.62 (259/260)	67.93 (161/237)	1	0.32	0.62	0.99	Family members of CD (controls=unaffected family members)
Balas, 1997; Spain	0.22	99.06 (210/212)	46.09 (342/742)	0.99	0.54	0.38	1	Known CD
Sumnik, 2000; Czech	0.07	100 (15/15)	87.63 (163/186)	1	0.12	0.08	1	Diabetes
Tuysuz, 2001; Turkey	0.52	90.91 (50/55)	32 (16/50)	0.91	0.68	0.76	0.87	Turkish Known CD
Neuhausen, 2002; Israel	0.31	100 (23/23)	86.54 (45/52)	1	0.13	0.34	1	Bedouin Arabs
Perez-Bravo, 1999; Chile	0.33	37.1 (23/62)	15.32 (19/124)	0.37	0.85	0.55	0.73	Chileans

Figure 24: HLA DQ2

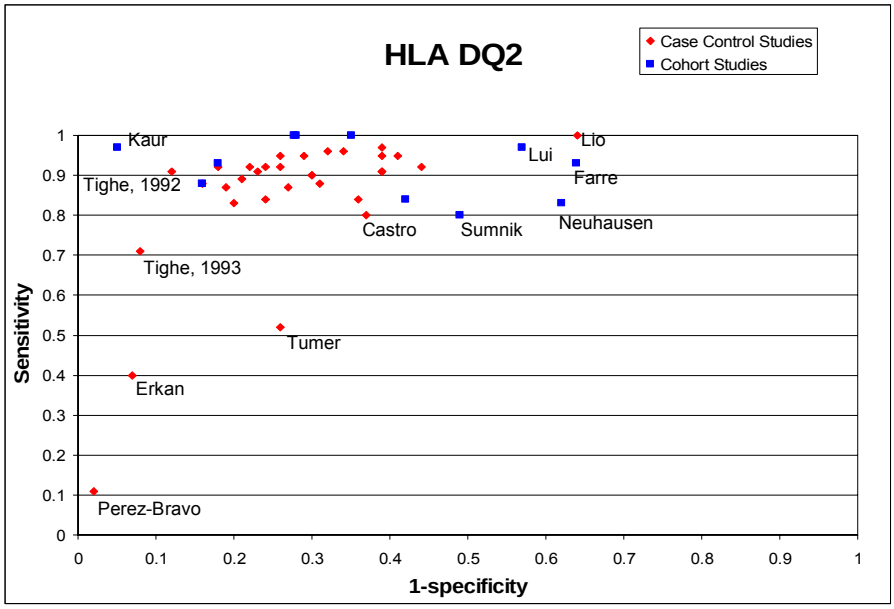


Table 34: Included studies of incidence of CD in the general population

Study	Country, period	Group at risk	Period related to results	Incidence	
				Crude incidence (# cases/100,000 patient year)	**Cumulative incidence** (# cases/1,000 births)
Ivarsson, 2003 Duplicate Ivarsson, 2000[193]	Sweden, 1973-97	Children	1997 (0-2 y)	51 (95% CI: 36-70)	Age 2 (1995): 1.7 (95% CI: 1.3-2.1)
			1996 (2-5 y)	33 (95% CI: 24-44)	
			1996 (5-15 y)	10 (95% CI: 7-13)	
Weile, 1993 Duplicate Weile, 1993[196]	Denmark, 1960-88	Children	1960-88		Age 5 (1988): 0.118
Maki, 1990 Duplicate ref[194]	Finland, 1960-84	Children	1974-83	3.46 (95% CI: n/r)	
Hawkes, 2000	England, 1981-95	Children	1991-95	2.15 (95% CI: n/r)	
Magazzu, 1994	Sicily 1975-89	Children	1989 birth cohort		Age 5 (1989): 1.16 95% CI: 0.92-1.42
Lopez-Rodriguez, 2003	Spain, 1981-99	Children 0-14 y	1981-90	6.87 (95% CI: 5.26-8.83)	
			1991-99	16.04 (95% CI: 12.99-19.59)	
		Children 0-4 y	1991-99	42.04 (95% CI: n/r)	
Hoffenberg, 2003	US (Denver, Colorado), 1993-99	Children	1993-99		Age 5 (1999): 9 (95% CI: 4-20)
Jansen, 1993	Netherlands 1990-92	All ages	1991-92	1.0 (95% CI: n/r)	
Corrao, 1995	Italy 1990-91	All ages	1990-91	2.13 (95% CI: n/r)	Age 5 (1991): 0.81
Talley, 1994	US 1960-90 Olmstead County	All ages	1960-90	1.2 (95% CI: 0.7-1.6)	
			1980-90	1.7 (95% CI: n/r)	
Bodé, 1996	Denmark, 1976-91	Adults	1976-91	1.27 (95% CI: n/r)	
Collin, 1997	Finland, 1975-94	Adults	1990-94	17.2 (95% CI: n/r)	
Hawkes, 2000	England, 1981-95	Adults	1991-95	3.08 (95% CI: n/r)	

Incidence in children: The crude incidence of CD in children age 0 to 15 years varied from 2.15 to 51 cases per 100,000 patient years.[193-195,198,201,204] When reported, the relative risk (RR) of CD was greatest for the 0- to 2-year age group, as well as for women, and varied from 32.26 to

Table 35: Prevalence of CD by country

Author, year	Country	Age group	Test	Total patients	Prevalence by serology	Prevalence by biopsy	Notes
Fasano, 2003	USA	Adults	EMA - ME; all positive EMA tested with tTG-HU	2,845	0.00949		116/350 biopsied
Green, 2000	USA	Adults	EGD/biopsy	1,749		0.00515	Not all sytematically biopsied; only those with suggestive endoscopic features
Not, 1998	USA	Adults	IgG- and IgA-AGA - ELISA; confirmed with IgA-EMA ME or HU	2,000	0.00400		
Fasano, 2003	USA	Children		1,281	0.00312		
Johnston, 1998	UK	Adults	IgA-AGA, IgA-EMA	1,823	0.00823		
Sanders, 2003	UK	Adults	IgG- and IgA - ELISA; EMA-ME	1,200	0.01917	0.01000	22/23 biopsied
West, 2003	U.K.	Adults	IgA EMA-ME, IgA-tTGA	7,527	0.01156		
Rutz, 2002	Switzerland	Children	IgA-EMA-ME, IgA-tTG, IgG-AGA and IgA-AGA	1,450	0.00759	0.00690	10/11 biopsied
Borch, 2001	Sweden	Adults	Biopsy, IgA- and IgG-AGA; IgA-EMA-ME	482	0.01452	0.01867	
Grodzinsky, 1996	Sweden	Adults	IgA-AGA; IgA-EMA	1,866	0.00589	0.00375	Prevalence by IgA-EMA not reported
Ivarsson, 1999	Sweden	Adults	IgA- and IgG-AGA - ELISA, cut-off not recorded; IgA-EMA - ME; serum IgA level	1,894	0.00475	0.00475	
Sjoberg, 1994	Sweden	Adults	IgG- and IgA-AGA	1,537	0.01431	0.00065	13/22 biopsied
Sjoberg, 1999	Sweden	Adults	IgA-AGA, IgA confirmed with EMA-ME	1970	0.00152	0.00152	

EGD=esophagogastroduodenoscopy; IF=immunofluorescence; prevalence expressed as proportion (multiply by 100 for percent, or 100,000 for per 100,000 value)

Table 35 (cont'd): Prevalence of CD by country

Author, year	Country	Age group	Test	Total patients	Prevalence by serology	Prevalence by biopsy	Notes
Carlsson, 2001	Sweden	Children	AGA, EMA, biopsy using Watson capsule	690	0.01884	0.01594	
Riestra, 2000	Spain	Adults	IgG/IgA-AGA, IgA-EMA; the study was conducted as a 1) two-step protocol (determination of IgA/IgG-AGA, if positive measuring IgA-EMA); and a 2) one-step protocol (measuring IgA-EMA)	1,170	0.00171	0.00256	1 CD picked up when AGA and EMA was neg.
Corazza, 1997	Republic of San Marino	Adults	IgA-EMA; biopsy	559	0.00179	0.00179	
Hovdenak, 1999	Norway	Adults	IgA- and IgG-AGA; IgA-EMA	2,069	0.00387	0.00338	
Rostami, 1999	Netherlands	Adults	IgA-EMA	1,000	0.00300	0.00300	
Csizmadia, 1999	Netherlands	Children	IgA-EMA	6,127	0.01224	0.00506	57/75 biopsied
Pittschieler, 1996	Italy	Adults	IgA- and IgG-AGA; IgA-EMA; biopsy	4,615	0.00195	0.00195	38 of 140 biopsied
Trevisiol, 1999	Italy	Adults	IgA-EMA; biopsy	4,000	0.00250	0.00250	
Volta, 2001	Italy	Adults (mostly)	IgA-EMA-HU; biopsy	3,483	0.00574	0.00488	Prevalence of 0.57% (20/3483) if included 3 patients with normal villous but with increased IELs
Catassi, 2000	Italy	Children	IgG-AGA (7 AU); IgA-AGA (15 AU); IgA-EMA indirect IF (1:5 dilution); biopsy	2,096	0.00859		
Catassi, 1996	Italy	Children	IgA- or IgG-AGA; confirmed with EMA and biopsy	17,201	0.00645	0.00477	

EGD=esophagogastroduodenoscopy; IF=immunofluorescence; prevalence expressed as proportion (multiply by 100 for percent, or 100,000 for per 100,000 value)

Table 35 (cont'd): Prevalence of CD by country

Author, year	Country	Age group	Test	Total patients	Prevalence by serology	Prevalence by biopsy	Notes
Di Pietralata, 1992	Italy	Children	IgA-AGA; biopsy	3,022	0.00629	0.00596	
Dickey, 1992	Ireland	Adults	IgA AGA	443	0.01129		
Jager, 2001	Germany	Mixed - mostly adults	IgA-AGA, IgG-AGA, IgA-tTG -	150	0.02667		Mixed group of at-risk populations, healthy group used
Kolho, 1998	Finland	Adults	EMA -HU	1,070	0.01028	0.00748	
Maki, 2004	Finland	Children	IgA and IgG tTG; IgA and IgG EMA - IF; total serum IgA; HLA DR, DQ2 and DQ8	3,654	0.01259	0.00739	
Collin, 2002	Finland	Mixed - mostly adults	Biopsy	2,974	0.00605		
Weile, 2001	Denmark and Sweden	Adults	Serum IgA: IgG-AGA; IgA-AGA, cut-off >40 units; EMA; in cases of IgA <0.07g/L, IgG-AGA was analyzed	1,573	0.00254		

EGD=esophagogastroduodenoscopy; IF=immunofluorescence; prevalence expressed as proportion (multiply by 100 for percent, or 100,000 for per 100,000 value)

Table 36: Prevalence of CD by serological screening test

Screening test	Age group	Number of studies	Total patients	Prevalence range
Primary biopsy	Adults	2[207,210]	4,723	0.00515 - 0.00605
IgA AGA	Overall	2[223,229]	3,465	0.00629 - 0.01129
	Adults	1[229]	443	0.01129
	Children	1[223]	3,022	0.00629
IgA / IgG AGA	Adults	1[216]	1,537	0.01431
IgA AGA - IGA EMA	Overall	6[208,209,211,217,219,226]	8,831	0.00152 - 0.01884
	Adults	5[208,209,211,217,219]	6,999	0.00152 - 0.01884
	Children	1[321]	1,823	0.00823
IgA/IgG AGA – IgA EMA	Overall	7[212,213,218,220,221,224,227]	30,648	0.00195 - 0.01917
	Adults	5[212,213,218,224,227]	11,351	0.00195 - 0.01917
	Children (Italy)	2[220,221]	19,297	0.00645 - 0.00859
IgA/IgG AGA – IgA tTG	Mostly adults (Germany)	1[234]	150	0.02667
IgA EMA	Overall	7[126,214,222,225,230-232]	17,409	0.00171 – 0.01224
	Adults	7[126,214,222,225,230,231]		0.00171 – 0.01028
	Children (Netherlands)	1[232]	6,127	0.01224
IgA EMA – IgG tTG	Overall	4[206,215,228,233]	16,757	0.00312 - 0.01259
	Adults (USA, UK)	2[206,228]	10,372	0.00949 - 0.01156
	Children	3 (includes Fasano Child Group)[206,215,233]	6,385	0.00312 - 0.01259
Note: Country of study was indicated when possible; prevalence expressed as proportion (multiply by 100 for percent, or 100,000 for per 100,000 value)				

Table 37: Prevalence of CD by statistical percentiles

Percentiles	Serology	Biopsy
5	.0016255	.0007378
10	.0018050	.0015761
25	.0030919	.0025321
50	.0063702	.0047672
60	.0084439	.0050768
75	.0117290	.0071429
80	.0125193	.0074416
90	.0184088	.0147536
95	.0225417	.0183992
100	.0266667	.0186722
Minimum	.00152	.00065
Maximum	.02667	.01867

Prevalence expressed as proportion (multiply by 100 for percent, or 100,000 for per 100,000 value)

Figure 26: Frequency distribution of prevalence of CD by serology among included studies

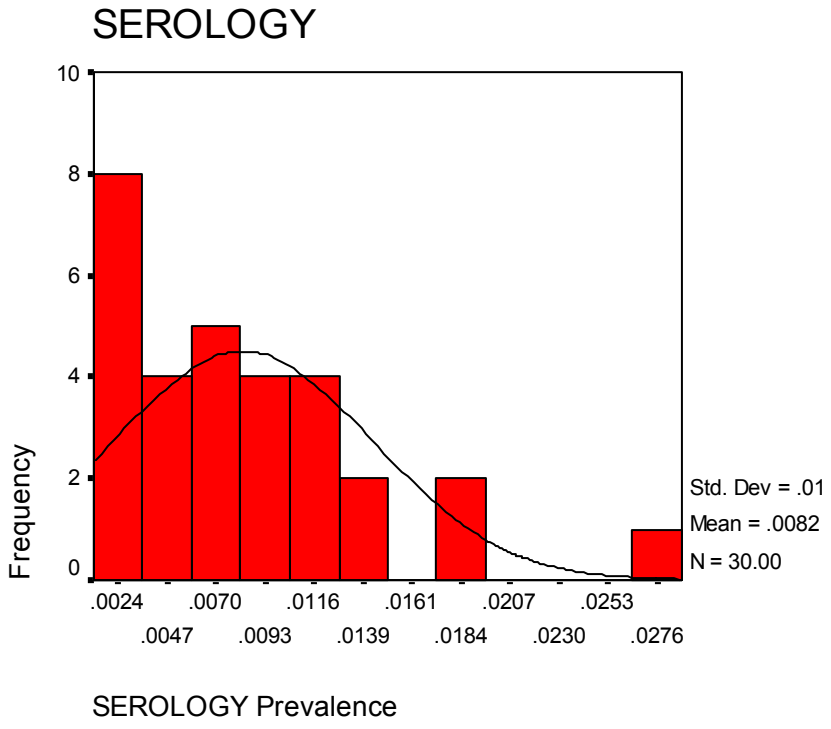


Table 38: Included studies for prevalence of CD in patients with suspected CD

Study, year; country	Clinical setting	Age group	Dx criteria	N tested	Prevalence (%)
Bardella, 1991; Italy	Referral center	Adults	Biopsy	60	43.3
Bardella, 2001; Italy	Referral center	Adults	Biopsy	80	50.0
Carrocio, 2002; Italy	Referral center	Adults	Biopsy	207	11.6
Fasano, 2003; USA	Not reported	Adults	EMA	1,910	1.5
Bode, 1993; Denmark	Referral center	Children	Biopsy	191	7.3
Day, 2000; New Zealand	Referral center	Children	Biopsy	153	4.6
Thomas, 1992; England	Referral center	Children	Biopsy	381	7.9
Chan, 2001; Canada	Referral center	Children	Biopsy	77	13.0
Chartrand, 1997; Canada	Referral center	Children	Biopsy	176	17.0
Ventura, 2001; Italy	Community pediatricians	Children	Biopsy	240	7.5
Fitzpatrick, 2001; Canada	Community pediatricians	Children	EMA	92	1.1
Fasano, 2003; USA	Not reported	Children	EMA	1,326	4.0
Hill, 2000; USA	Referral center	Children	EMA	1,008	2.5
Hin, 1999; England	Community practice	All ages	Biopsy	1,000	3.0

Prevalence of CD in with Type I Diabetes

The literature search identified 36 studies that assessed the prevalence of CD in patients with type I diabetes (insulin-dependent diabetes mellitus [IDDM]).[191,192,234,250-282] Two sets of duplicate publications were identified.[191,192,277,282] The publications with the most complete data sets were used.[277,282] Of the 34 unique studies (Evidence Table 6, Appendix I; Table 39), seven were conducted in an adult population,[257,263,266,270,273,277,279] 21 in a child population,[250-252,254-256,260-262,264,265,267,271,272,274-276,278,280-282] and six were conducted in a mixed population of adults and children.[234,253,258,259,268,269]

All the included studies initially screened the study population with one or more antibodies. Three studies did not confirm positive serology with biopsy,[265-267] whereas in nine studies confirmatory biopsies were performed in less than 75% of the screened-positive patients.[253,259,264,269,272,274,277-279] These studies were not included in the pooled estimates of the prevalence of CD by biopsy. All the studies that reported biopsy criteria used partial villous atrophy or greater to define CD.

Table 39: Included studies of prevalence of CD in type I diabetes

Author, year; country	Total patients	Age group	Screening test(s)	First serology	Confirmatory serology	Biopsy proven	Biopsy criteria & description	Prevalence by serology	Prevalence by biopsy	Notes
Li Voon Chong, 2002; UK	509	Adults	EMA	7	None	n/a	None done	0.0138	n/a	
Talal, 1997; USA	185	Adults	EMA	9	None	4	ESPGAN	0.0486	0.0216	Only 5/9 biopsied
Rossi, 1993	211	Children, some adults	EMA	10	None	3	ESPGAN	0.0474	0.0142	Only 3/10 biopsied
Kaukinen, 1999; Finland	62	Adults	EMA		None	7	ESPGAN	0.0000	0.1129	
Sjoberg, 1998; Germany	848	Adults	AGA - IgG or IgA; EMA	258	22	7	Marsh	0.0259	0.0083	Only 14/22 biopsied
Sategna-Guidetti, 1994; Italy	383	Adults	EMA	12	None	10	Roy-Choudhury	0.0313	0.0261	10/12 biopsied
Rensch, 1996; USA	47	Adults	EMA	3	None	3	Loss of villous architecture, crypt hyperplasia, and increased IELs	0.0638	0.0638	
Frazer-Reynolds, 1998; Canada	263	Children	EMA	17	None	12	Carey capsule; Marsh criteria;	0.0646	0.0456	17/19 biopsied
Gillett, 2001; Canada	233	Children	EMA or AGA	19	None	14	Not reported	0.0815	0.0601	18/19 biopsied
Hansen, 2001; Denmark	104	Children	EMA or tTG	10	None	9	Partial or total villous atrophy, crypt hyperplasia and IEL infiltration	0.0962	0.0865	9/10 biopsied
Saukkonen, 1996; Finland	776	Children	AGA or ARA	76	None	19	Not reported	0.0979	0.0245	Only 35/76 biopsied
Spiekerkoetter, 2002; Germany	205	Children	tTG IgA or IgG	13	None	6	Marsh	0.0634	0.0293	Only 8/13 biopsied

Table 39 (cont'd): Included studies of prevalence of CD in type I diabetes

Author, year; country	Total patients	Age group	Screening test(s)	First serology	Confirmatory serology	Biopsy proven	Biopsy criteria & description	Prevalence by serology	Prevalence by biopsy	Notes
Arato, 2003; Hungary	205	Children	EMA	24	None	17	n/r	0.1171	0.0829	
Barera,1991; Italy	498	Children	AGA IgA then if neg IgG AGA	30	None	16	Subtotal villous atrophy	0.0602	0.0321	22/30 biopsied
Barera, 2002; Italy	273	Children	EMA, second EMA	15	10	9	Marsh; type II or III lesion	0.0549	0.0330	
Valerio, 2002; Italy	383	Children	EMA or IgG AGA	n/r	None	32	ESPGAN	n/r	0.0836	
Carelo, 1996; Spain	141	Children	IgA AGA if positive on two occaions	12	None	4	Subtotal villous atrophy	0.0851	0.0284	
Roldan, 1998; Spain	177	Children	IgA, IgG AGA, (and known cases, and some tested with EMA)	19	None	7	ESPGAN	0.1073	0.0395	Mixed group diagnosed by different means
Juan, 1998; Spain	93	Children	EMA	7	None	6	ESPGAN	0.0753	0.0645	
Sigurs, 1993; Sweden	459	Children	AGA	19	None	21	Watson Capsule	0.0414	0.0458	18/19 biopsied included known CD
Agardh, 2001; Sweden	162	Children	AGA, EMA, or tTG IgG or IgA	8	8	6	As described by Carlsson et al. 1999, Pediatrics 103:1248	0.0494	0.0370	Only 6 of 8 biopsied
Acerini, 1998; UK	167	Children	EMA or AGA	11	None	8	ESPGAN	0.0659	0.0479	9/11 biopsied
De Block, 2001; Belgium	399	Mixed	EMA	9	None	3	No biopsy performed	0.0226	0.0075	Unclear how the 3 cases confirmed

Table 39 (cont'd): Included studies of prevalence of CD in type I diabetes

Author, year; country	Total patients	Age group	Screening test(s)	First serology	Confirmatory serology	Biopsy proven	Biopsy criteria & description	Prevalence by serology	Prevalence by biopsy	Notes
Jager, 2001	197	Mixed	tTG	19	None		n/r	0.0964		
De Vitis, 1996; Italy	1114	Mixed	IgA, IgG then IgA EMA	121	55.00	63	Marsh - "villous atrophy"	0.1086	0.0566	78/121 biopsied
Not, 2001; Italy	491	Mixed	EMA	28	None	28	Intestinal biopsy; Marsh's modified classification	0.0570	0.0570	
Bao, 1999; USA	847	Mixed	tTG	98	None	15	n/r	0.1157	0.0177	Only 20/98 biopsied
Kordonouri, 2000; Germany	520	Mixed - mostly children	tTG	23	None	9	Marsh criteria	0.0442	0.0173	10/23 not biopsied
Aktay, 2001; USA	218	Mixed - mostly children	EMA	17	None	10	Partial or total villous atrophy, inflammation in lamina propria with increased IELs, and hyperplasia of crypts; classified as partial or total villous atrophy	0.0780	0.0459	14/17 biopsied
Cronin, 1997; Ireland	101	Mixed - mostly adults	EMA	8	None	5	n/r	0.0792	0.0495	
Schober, 2000; Austria	403	Mixed - mostly children	EMA	12	None	6	Modified Marsh and Crowe; Watson-type capsule	0.0298	0.0149	11/12 biopsied
Lampasona, 1999; Italy	287	Mixed - mostly children	tTG IgA or IgG	24	None	n/a	No biopsy	0.0836	n/a	

Table 39 (cont'd): Included studies of prevalence of CD in type I diabetes

Author, year; country	Total patients	Age group	Screening test(s)	First serology	Confirmatory serology	Biopsy proven	Biopsy criteria & description	Prevalence by serology	Prevalence by biopsy	Notes
Lorini, 1996; Italy	133	Mixed - mostly children	AGA IgA or IgG	5	None	n/a	No biopsy	0.0376	n/a	
Page, 1994; Mixed	1785	n/a	AGA	73	None	13	n/a	0.0409	0.0073	Only 49/73 biopsied

Table 40: Summary of prevalence of CD in type I diabetes by age groups and screening test

Number of studies	Total patients	Age group	Screening test(s)	Prevalence by serology	Prevalence by biopsy
1[277]	848	Adults	AGA - IgG or IgA; then EMA	0.0259	0.0083*
1[266]	509	Adults	EMA	0.0138	n/a
1[279]	185	Adults	EMA	0.0486	0.0216*
1[263]	62	Adults	EMA	n/a	0.1129
3[257,270,273]	531	Adults	EMA	0.0433	0.0339
1[274]	776	Children	AGA or ARA	0.0979	0.0245*
1[276]	459	Children	AGA	0.0414	0.0458
4[254,256,267,271]	949	Children	AGA – various combinations	0.0695	0.0331
1[252]	205	Children	EMA	0.1171	0.0829
1[275]	403	Children	EMA	0.0298	0.0149
5[251,255,260,272,281]	1058	Children	EMA	0.0624	0.0437
4[251,255,260,281]	847	Children	EMA	0.0661	0.0437
5[250,261,262,280,282]	1049	Children	EMA - combinations	0.0721	0.0658
1[265]	287	Children	tTG IgA with IgG	0.0836	n/a
1[278]	205	Children	tTG IgA with IgG	0.0634	0.0293*
1[264]	520	Children	tTG	0.0442	0.0173*
1[269]	1785	Mixed	AGA	0.0409	0.0073*
1[259]	1114	Mixed	IgA, IgG-AGA then IgA-EMA	0.0494	0.0566*
1[268]	491	Mixed	EMA	0.0570	0.0570
1[258]	399	Mixed	EMA	0.0226	0.0075†
1[234]	197	Mixed	tTG	0.0964	n/a
1[253]	847	Mixed	tTG	0.1157	0.0177*

*large proportion of serology-positive patients not biopsied,[253,259,264,269,272,274,277-279] these were not included in the pooled analysis of prevalence by biopsy
**no description of how diagnosis made – result not pooled

Table 41: Prevalence of CD in relatives of CD patients

Study, year; country	Relative Type	Index case	Screening	Dx criteria	N tested	Prevalence (%)
Polvi, 1996; Finland	1st degree	CD in family	Biopsy	ESPGAN	90	20
Holm, 1993; Finland	1st degree	CD in family	Biopsy	Some VA	121	10.7
Robinson, 1971; England	1st degree	CD child in family	Biopsy	Some VA	29	10.3
Rolles, 1974; England	1st degree	CD child in family	Biopsy	Not reported	72	5.6
Stokes, 1976; England	1st degree	CD in family	Biopsy	Some VA	182	22.5
Tursi, 2003; Italy	1st degree	CD in family	Biopsy	Marsh I-IV	111	44.1
Corazza, 1992; Italy	1st degree	CD adult in family	AGA	Some VA	328	4.0
Pittschieler, 2003; Italy	1st degree	CD in family	EMA, TTG	Some VA	92	12.0
Rostami, 2000; Netherlands	1st degree	CD in family	AGA, EMA, Hx	ESPGAN	338	10.9
Hogberg, 2003; Sweden	1st degree	CD in family	AGA, EMA, TTG	Some VA	120	8.3
Korponay-Szabo, 1998; Hungary	1st degree	CD in family	EMA	Some VA	943	9.1
Farre, 1999; Spain	1st degree	CD in family	AGA, EMA	Some VA	675	5.6
Kotze, 2001; Brazil	1st degree	CD in family	EMA	+ve serology*	115	3.5
Fasano, 2003; US	1st degree	CD in family	EMA	+ve serology	4,508	4.5
Vitoria, 1994; Spain	1st degree	CD in family	AGA, EMA	+ve serology	642	2.8
Mustalahti, 2002; Finland	1st degree	>1 DH or CD sib	AGA, EMA	+ve serology	466	9.4
Book, 2003; US	1st degree	CD sib pairs	EMA, TTG	+ve serology	163	17.2
Hill, 2000; US	1st & 2nd degree	CD in family	EMA	+ve serology	192	4.7
Fasano, 2003; US	2nd degree	CD in family	EMA	+ve serology	1,275	2.6
Korponay-Szabo, 1998; Hungary	2nd degree	CD in family	EMA	+ve serology	54	5.6
Book, 2003; US	2nd degree	CD sib pairs	EMA, TTG	+ve serology	82	19.5
Book, 2003; US	1st cousins	CD sib pairs	EMA, TTG	+ve serology	47	17.0

*EMA titre $\geq$ = 1/5
VA = villous atrophy; DH = dermatitis herpetiformis

Table 42: Included studies of CD in adult patients with anemia

Author, year; country	No. of pts	Age group	Population	Anemia type	Screening test	First serology	Confirmatory serology	Biospsy proven	Biopsy criteria	Prevalence by serology	Prevalence by biopsy
Akerman, 1996; Israel	93	Adult - some teens	Out-patients with IDA (50% symptomatic)	IDA	EGD/ biopsy			13	Subtotal or greater villous atrophy	n/a	0.139785
Annibale, 2001; Italy	71	Adults	Asymptomatic	IDA	EGD/ biopsy			4	Marsh	n/a	0.056338
Corazza, 1995; Italy	200	Adults	Referred to hematology	IDA	IgA/IgG-AGA then EMA then biopsy	16	10	10	Not mentioned	0.05	0.05
Dickey, 1997; UK	10	Adults	Asymptomatic, previously investigated no gross GI cause found	IDA	IgA AGA then EMA	4	3		Endoscopic biopsy; criteria n/r; finding of villous atrophy and IELs in duodenal biopsy	0.3	n/a
Howard, 2002; UK	258	Adults	IDA identified through lab	IDA, folate	IgA/IgG-AGA and EMA then biopsy	28		12	Not applicabe	0.10852713	0.046512*
Kepczyk, 1995; USA	39	Adults	Mostly symptomatic out-patients with IDA	IDA	EGD/ biopsy			4	Villous atrophy, crypt hyperplasia, inflammatory infiltrate	n/a	0.102564
McIntyre, 1993; UK	50	Adults	Out-patients with IDA	IDA	EGD/ biopsy			3	Not reported	n/a	0.06

*24/28 biopsied

Table 42 (cont'd): Included studies of CD in adult patients with anemia

Author, year; country	No. of pts	Age group	Population	Anemia type	Screening test	First serology	Confirmatory serology	Biospsy proven	Biopsy criteria	Prevalence by serology	Prevalence by biopsy
Oxentenko, 2002; USA	113	Adults	Undergoing EGD for IDA	IDA	EGD/ biopsy			17	CD was defined as total or partial villous atrophy with IELs	Not applicable	0.150442
Ransford, 2002; UK	484	Adults	Referred to hematology	IDA	EMA then EGD/ biopsy	17		11	Revised ESPGAN; duodenal histologic changes were graded according to Marsh I-III	0.03512397	0.022727[†]
Unsworth, 2000; UK	483	Adults	Blood donors	Anemia unspecified	IgA-EMA then biopsy	32		22	n/r	0.06625259	0.045549[‡]
Annibale, 2003; Italy	59	Adult	Pre-menopausal women with IDA	IDA	IgA tTG then biopsy	7		5	Marsh	0.11864407	0.084746[**]
Van Mook, 2001; The Netherlands	35	Adult	Asymptomatic	IDA	EGD / biopsy			1	Marsh I	Not applicable	0.028571

[†]5 Marsh I identified by CD3
[‡]25/32 biopsied
[**]5/7 biopsied; 30 had heavy periods; CD in 1/22 with heavy periods, and 4/18 with normal periods

Table 43: Summary of prevalence of CD in adult patients with anemia by population and screening test

No. of studies	Total patients	Population	Screening test(s)	Prevalence by serology	Prevalence by biopsy
3[283,288,290]	245	Symptomatic IDA	Biopsy	n/a	0.139
1[286]	10	Asymptomatic, previously no gross GI cause found investigated	IgA-AGA then EMA	0.3	n/a
1[293]	59	Pre-menopausal women with IDA	IgA-tTG then Biopsy	0.119	0.085
4[285,287,291,292]	1,425	Asymptomatic serology screened	IgA-EMA, or-AGA followed by EMA; all biopsy confirmed	0.061	0.039
3[284,289,294]	156	Asymptomatic biopsy screened	Biopsy	n/a	0.051

Prevalence of CD in Patients with Low Bone Mineral Density (BMD)

Four articles were identified that assessed the prevalence of CD in patients with low BMD (Evidence Table 9, Appendix I).[295-297,326] The study characteristics and definitions used to define low BMD, osteopenia, and CD are presented in Table 44. Three of these studies determined BMD using dual energy X-ray absorptiometry (DXA), and defined osteoporosis as a BMD less than 2.5 standard deviations from the peak bone mass of sex-matched control,[295,297,326] whereas, the other used single photon absorptiometry (SPA).[296] One study included patients with non-traumatic fractures,[295] whereas, in the others, idiopathic osteoporosis was sufficient for inclusion. All four studies used serology screening with biopsy confirmation of screen-positive patients. Three studies relied on AGA testing as the initial screen[295,296,326] followed by biopsy,[296] or further confirmatory serology testing with EMA[295] or tTG[326] prior to biopsy. The final study screened with EMA-ME, with positive screens moving on to biopsy.[297] Two studies defined the biopsy criteria for CD and used a fairly standard but rigid requirement of subtotal or greater villous atrophy.[295,297]

In the studies that used this test as the initial screen, AGA was positive in 6% to 21% of the patients with osteoporosis. However, in these studies CD was confirmed by biopsy in only 0.9% to 3% of patients.[295,296,326] The study that used EMA-ME as a screening test identified potential CD cases in 7.3% of patients, but none of these met the authors' biopsy criteria for CD.[297]

Table 44: Prevalence of CD in patients with low BMD

Author, year; country	Population	BMD definition	Test	Prevalence
Lindh, 1992, Sweden	92 consecutive patients with idiopathic osteoporosis screened for CD; 91% F (mean age 66+-12 Y); and 9 M (mean age 50+-12 Y)	Bone mineral content by photon absorptiometry (SPA) of non-dominant forearm; criteria n/r	IgA-AGA ELISA; cut-off was 2 SD above the mean of blood donors; confirmatory biopsy in 6 - criteria n/r	11/92 (12.0%) AGA +ve.; 3% (3/92) biopsy confirmed Mean proximal SPA 0.97 g/cm^2 Mean distal SPA 0.67 g/cm^2
Gonzalez, 2002; Argentina	127 postmenopausal women with osteoporosis; age (Y): mean 68, range 50-82; 747 controls; age (Y): mean 29, range 16-79	History of non-traumatic fractures and lumbar spine and/or femoral neck BMD below T-score -2.5 DXA	IgA and IgG-AGA ELISA; cut-off levels: for IgA - 15 AU/mL; for IgG - 20 AU/mL; positives confirmed with IgA-EMA-ME positive at 1:5 dilution; positives confirmed with biopsy in EMA positives; showing villous atrophy, crypt hyperplasia and IEL >30%	1/127, or 7.9 x 1000 (95% CI: 0.2-43.1); test positivity: AGA found in 8 of 127 (6.3%) pts on level 1; 1 of these 8 pts was EMA positive on the 2nd level and eligible for biopsy which established a diagnosis of CD in 1 (0.9%)
Mather, 2001; Canada	Idiopathic low BMD; mean age 57 Y; range 18-86 Y; 81.3% (78) F; 18.7% M (18) All osteopenic; 45/78 F and 13/18 M osteoporotic	DXA Osteopenia: BMD <1 SD of mean sex-matched peak BMD Osteoporosis: BMD <2.5 SD of mean sex-matched peak BMD	IgA- EMA-ME titers of ≥1:10; and biopsy confirmation based on subtotal or greater villous atrophy	7 (7.3%) of 96 pts were EMA +ve; all biopsies were negative based on subtotal or greater villous atrophy prevalence of 0%
Nuti, 2001; Italy	255 females with osteoporosis; mean age 66.6 Y range 36-65 Y	DXA BMD below T-score -2.5	IgA-AGA ELISA-cut-off level of 10 AU/mL-1; IgA-tTg cut-off >22 AU; confirmatory biopsy criteria n/r	53/255 (20.8%) +ve IgG-AGA; 24/53 +ve for tTG antibody (9.4%); intestinal biopsy in 10/24 resulted in 6 (2.4%) with confirmed CD
F=female; M-male; DXA=dual X-ray absorptiometry; Y=years; n/r=not recorded				

Quality Assessment

Using the cross-sectional checklist, the overall quality of reports of the included studies for the Celiac 2 objective, was marginal to fair (Appendix J, Table 2). For example, most of the studies did not report on whether the patients were consecutively enrolled, which could possibly lead to selection bias.

Table 45: Included studies for risk of lymphoma in CD

Study, year; country, period	Study type	Participants	Risk of lymphoma	Mortality	Other observations
Cottone, 1999; Sicily, 1980-97	Retrospective cohort	• 228 CD patients • 76% females • mean age at Dx 34.7 • 98% adult Dx • 100% on strict GFD	• Incidence NHL 3.1% • SIR NHL 3.75, p <0.01	SMR all causes 3.8 (1.9-6.7)	
Holmes, 1989; England, 1941-85	Prospective cohort	• 210 CD patients • 55% females • 51% on strict GFD	• Incidence NHL 4.3% • SIR NHL 42.7 (19.6-81.4)	SMR not reported	SIR NHL vs GFD compliance: • Strict GFD 44.4 • Gluten diet 100
Logan, 1989; Scotland, 1979-1986	Prospective cohort	• 653 CD patients • 60% females		Mortality from NHL 2.6% SMR from lymphoma 31 p<0.001 SMR all causes 1.9 (1.5-2.2)	SMR childhood Dx 1.4 (0.4-3.7) SMR adult dx 1.9 (1.5-2.3)
Askling, 2002; Sweden, 1964-94	Retrospective cohort	• 11,019 CD patients • 59% females • Mean age at Dx 17.4 (range 0->70)	• Incidence NHL 0.34% • SIR NHL 6.3 (4.2-125)	SMR from NHL 11.4 (7.8-16) SMR all causes 2 (1.8-2.1)	SIR NHL childhood Dx 1.9 (0.4-5.5) SIR NHL adult Dx 7.0 (5.0-9.5)
Collin, 1996; Finland, 1970-93	Prospective cohort	• 383 CD patients • 73% females • Mean age at Dx 41.8 (range 16-78) • 75% on strict GFD	• Incidence NHL 0.26% • SIR NHL 2.66 (0.07-14.8)		
Corrao, 2001; Italy, 1962-94	Prospective cohort	• 1,072 CD patients • 76% females • mean age at Dx 35.7 (range 18->50) • 59% on strict GFD		SMR from NHL: 69.3 (40.7-112.6) SMR all causes: 2.0 (1.5-2.7)	SMR age 18-29 at Dx: 2.5 (0.5-7.3) SMR age 30-49 at Dx: 2.4 (1.3-4.0) SMR age >50 at Dx: 1.9 (1.3-2.6) SMR strict GFD: 0.5 (0.2-1.1) SMR unlikely GFD: 6.0 (4.0-8.8)
Green, 2003; USA, 1981-2000	Prospective cohort	• 381 CD patients • 64% females • mean age at Dx 44 +/- 18	• Incidence NHL 1.3% • SIR NHL 6.2 (2.9-14)		
Selby, 1979; Australia, 1959-78	Retrospective cohort	• 93 CD patients • 67% females • mean age at Dx 40 (range 14-70)	• Incidence NHL 4.3% • SIR NHL 4.94, p<.0005		
Delco, 1999; USA, 1986-95	Case-control	• 458 CD patients • 4% females	• OR NHL 4.53 (2.01-10.23)		
Dx=diagnosis; SIR=standardized inidence ratio; NHL=non-Hodgkin's lymphoma; SMR=standardized mortality					

Table 46: Results of study assessing γδ+ IELs in patients with and without CD[136]

Test	Celiac (n=27)	CD excluded on biopsy (n=79)	Biopsy-negative controls (n=28)
Mean # of γδ+ IELs	40.4 (95%CI: 32.7-48.2)	6.7 (95%CI: 4.8-8.5)	1.6 (95% CI: 1.1-2.1)
Elevated γδ+ IELs (> 4.4 cells/mm)	27 (100%)	39 (49%)	n/a
AGA positive	21/26 (81%)	33/66 (50%)	n/a
Reticulin antibodies	27/27 (100%)	18/78 (23%)	n/a
HLA DQ2	19/21 (90%)	20/67 (30%)	

The mean density of γδ+ IELs was significantly greater in CD patients compared with those patients where CD was excluded on biopsy, and compared with biopsy-negative controls. The density of these IELs was also significantly higher in patients with CD excluded on biopsy compared with controls. Because the authors used the ESPGAN criteria, which requires some degree of villous atrophy, the 50% of subjects with CD excluded based on this criteria who were AGA positive begs the question of how many of these were actually CD patients. However, based on the reported data, elevated γδ+ IELs were calculated to have a sensitivity of 100%, but a specificity of only 50.6%, although the true specificity is likely higher. In the biopsy-negative suspected CD group, 66 out of the 79 underwent testing for HLA DQ2. Out of these patients, 46 tested negative for HLA DQ2. Given the high NPV of this test, it is likely that most of those patients do not have CD. Recalculating the specificity based on this assumption would raise its value, but unfortunately a breakdown of the number of patients with normal and elevated IEL in relation to HLA DQ2 was not reported. In any case, a better comparison would have been with the biopsy-negative control subjects, but the number of control subjects with raised IELs is not reported. Based on the mean density of IELs in this group, the number of patients with elevated IELs is likely to be low. During follow-up of the children suspected of having CD, but with normal mucosal biopsy and positive serology, four patients developed CD and responded to a GFD, further suggesting that this "control" group of patients with CD "excluded" on biopsy likely contained true CD patients who did not have villous atrophy. The results also suggest that the measurement of γδ+ IELs can be valuable in the diagnosis of CD, and hints at the fact that the requirement of villous atrophy on biopsy may miss some subjects with CD, particularly if they have raised IEL levels , positive serology and are HLA DQ2 positive.

Kutlu et al.[443] also studied the density of γδ+ IELs in untreated CD, treated CD and control patients (Table 47). The study population was made up of five children with classic CD with total villous atrophy and improvement on a GFD (Group A), seven patients studied after 1 to 11 years of a GFD with mucosal recovery (Group B), and 22 patients with CD by ESPGAN criteria who were left on a normal diet for 1 month to 10 years (Group C). The control group consisted of 15 children with various GI disorders other than CD, and 15 adults undergoing intestinal surgery for gastric and pancreatic disorders. The report aggregated data from groups A and C.

Table 47: Results of study assessing density of γδ+ IELs in patients with untreated CD, treated CD and control patients[443]

	Sub-total/total villous atrophy (n=18)	Moderate villous atrophy (n=7)	Normal mucosa (n=9)	Pediatric controls (n=15)	Adult controls (n=15)
Diet	normal		GFD	n/a	
γδ+ IELs/100 ECs	14.8	17.5	14.5	3.1	3.6

The density of γδ+ IELs/100 enterocytes was significantly higher in CD patients (15.4, n=34) compared with pediatric and adult control patients (3.1 and 3.6, respectively). However, the density did not correlate with histologic grade or with a GFD. Unfortunately, this study has several methodological flaws, and estimates of the sensitivity and or specificity of IEL in CD could not be derived. However, the study does indicate the potential usefulness of measuring γδ+ IELs in the overall evaluation of biopsy specimens for possible CD, and again demonstrates that CD patients can have a biopsy with normal villous structure which can be distinguished from normals by assessing the number of IELs.

In an interesting comparative study of the correlation of IELs with AGA positivity by ELISA, O'Farrelly et al.[444] studied 25 patients who had typical histologic features of CD and who were subsequently placed on a GFD. Ten of these were AGA positive, whereas 15 were negative. The second group consisted of 28 subjects suspected of CD but with "normal" small bowel histology. Twelve were AGA positive and 16 were negative. Increased levels of IELs were seen in both AGA positive (82.5) and negative (74.3) CD patients (difference not significant). On the other hand, among those with "normal" histology, AGA positive subjects had a significantly higher density of IELs than those who were AGA negative (42.4 vs 17, $p<0.001$). This data suggests that subjects suspected of CD with normal villous atrophy who have raised IEL densities should be further evaluated for CD, especially if serology is positive. These are also the types of patients where response to a GFD may be invaluable to firmly establish the diagnosis and help clarify the diagnostic value of low-grade histologic lesions.

Saputo et al.[445] compared the density of IELs between patients with confirmed CD, those undergoing investigation for CD, and control subjects (Table 48). The normal IEL range was determined to be between 4.68 and 17.60 based on the control group mean +/- 2 SD.

Table 48: Results of study comparing density of γδ+ IELs in patients with confirmed CD, those undergoing investigation for CD, and control subjects[445]

	Confirmed CD (n=9)	CD under investigation (n=40)	Controls (n=143)
IELs/50 ECs	68.55	51.21	11.14
# with raised IELs (estimated from figure)	9	40	2

These results again suggest the usefulness of IELs in the evaluation of histology of patients being assessed for CD, and suggest a sensitivity of raised IELs of 100%, and a specificity of 98.6%. Unfortunately, the authors do not report the number of individuals under investigation for CD who actually ended up having CD, so as to estimate the diagnostic parameters in this group.

Similarly, Jarvinen[436] studied IEL density and villous/crypt ratio in 928 Finnish patients with a suspicion of CD, and 59 biopsy-negative controls with dyspepsia (Table 49). CD was diagnosed on the basis of a suggestive small intestinal biopsy showing some degree of villous atrophy with subsequent later improvement on GFD. The main results excluding DH patients are presented below.

Table 49: Results of study comparing IEL density and villous/crypt ratio in patients with a suspicion of CD, and 59 biopsy-negative controls with dyspepsia[436]

	Untreated CD (n=138)	Treated CD (n=198)	Suspicion of CD with normal villi (n=545)	Controls (n=59)
CD3 + IELs	68*	40*	26	30
γδ+ IELs	19.8*	12*	3.2	2.3
Villous/crypt ratio	0.6*	1.9*	2.8	3.0
*statistically different from control				

The authors noted that using a cut off of 37 cells/mm for CD3+ and 4.3 cells/mm for γδ+ IELs, the sensitivities and specificities were 93% and 73% for CD3+, and 93% and 88% for raised γδ+ IELs, respectively. The PPVs and NPVs for raised γδ+ IELs were 95% and 85%, respectively, in this population. However, these results are based on the well-documented clear-cut CD group, and did not take into consideration the CD patients that might be in the suspicious but normal villi group. Among the patients with a suspicion of CD but normal villi and high γδ+ IELs (>4.3), 28% were EMA positive compared with only 8% with normal γδ+ IELs (<4.3). Unfortunately, the outcomes of these patients are not reported, so one cannot comment further based on this study about the usefulness of IELs in Marsh I or II patients.

Mino et al.[446] assessed the density of IELs in routinely stained specimens compared with specimens stained with the readily available CD3 antibody. Twenty-eight subjects with architecturally normal duodenal biopsies, which were well-oriented and demonstrated greater than 20 IELs/100 ECs were included in the study. AGA, EMA and tTG antibodies were measured. Subjects were divided in the groups listed in Table 50. Controls consisted of seven normal individuals, two patients with reflux, and two patients with irritable bowel syndrome.

Table 50: Results of study assessing IEL density in routinely stained specimens compared with specimens stained with the CD3 antibody[446]

	CD (n=8)	Treated CD (n=4)	Non-CD (n=16)	Controls (n=11)
Mean age	33.5	46.3	46.4	39.1
IELs/100 ECs by H&E staining	42.1	29.2	36.8	Not increased
IEL/100 ECs in villous tip by CD 3 staining	47.5	29.4	33.2	8.2

There were no statistically significant differences between any of the groups when IELs were measured with H&E staining. However, all pair-wise comparisons were statistically different, except between the treated CD group and the non-CD group, when villous-tip IELs were counted with CD3 staining. The authors conclude that villous tip IELs are more specific indicators of CD, particularly with CD3 staining (which is more readily available than staining for γδ+ IELs),

and suggest that the specificity of low grade Marsh lesions could be improved by these techniques.

In a similar study, Goldstein et al.[447] compared IEL density and villous distribution among patients suspected of CD. Twelve patients were diagnosed with CD based on histologic features and response to a GFD, whereas in 66 patients the diagnosis of CD was excluded based on biopsy, and supported by negative serology (and in some cases a lack of response to a GFD). Control cases consisted of patients with dyspepsia who underwent endoscopy and biopsy. The main results are summarized in Table 51.

Table 51: Results of study comparing IEL density and villous distribution among patients suspected of CD[447]

	CD (n=12)	Non-CD (n=66)	Controls (n=24)
Mean age	35.2	36.1	34.5
Iga EMA	8	3 (no response to GFD)	n/a
IgA AGA	5	13 (all EMA neg.)	n/a
Villous tip IELs	11.6	4.3	2.2
IELs distributed evenly along the villi	9/12 (75%)	3/68 (4%)	0
n/a = not applicable			

The authors found that the mean villous tip IEL density was significantly greater in the CD group than in the non-CD and control group. A more even distribution of IEL along the villi was also found to be significantly more common in the CD group compared with the other groups. However, this last point is controversial. Unfortunately, given that this is a small study, the authors did not look at differences in these characteristics among CD patients with different histologic grades.

Kuitumen et al.[448] compared the histologic features of children with untreated CD, treated CD, other GI disorders (cow's milk allergy, DH, congenital lactase deficiency, acrodermatitis enteropathica, and giardiasis) and a group of control subjects without GI pathology. Of the 52 children with CD in this group, all had severe villous atrophy. CD patients had the lowest enterocyte height, and the most intense IEL infiltration of the studied groups. The authors found no overlap between CD patients and controls for the density of IELs, villous height, crypt depth, and villous height to crypt depth; all these parameters were statistically different between the CD patients and controls.

Kaukinen et al.[449] studied 96 consecutive adults found to be ARA or AGA positive and compared them with 27 ARA- and AGA-negative patients with dyspepsia. All patients underwent duodenal biopsy and CD was diagnosed on the basis of a villous height to crypt depth of less than two and crypt hyperplasia. Twenty-nine patients met their biospsy criteria of CD (18 ARA- and AGA-positive patient, nine ARA-positive patients, and two AGA-positive patients). The 29 CD patients were placed on a GFD and of the 21 who were rebiopsied at 6 to 12 months, all showed unequivocal histologic improvement. The mean density of IELs in CD, serology positive, biopsy negative, and control patients were 87, 38, and 25 cells/mm, respectively. These numbers were statistically different. The mean density of $\gamma\delta$+ IELs among the CD patients was 16.6. Eleven serology-positive patients with normal villous structure (presumably Marsh I and II) expressed HLA DR and had higher levels of $\gamma\delta$+ IELs (mean of 13.4 cells/mm) than the non-CD controls. A repeat biopsy (time unspecified) was performed in 12 serology-positive patients

misclassified as having CD, then the specificity would drop to a still respectable 83%. Clearly, this type of study is the starting point in assessing the diagnostic parameters of the biopsy itself as a test. However, what is needed to fully assess biopsy as a test is a clearer measure of the false positive and negative rates. This can only be accomplished by using a battery of tests (biopsy, serology, HLA) to act as a gold standard to initially identify all potential cases, and then a follow-up period (response to GFD or gluten challenge) to assess the permanence of the diagnosis and the utility of biopsy at various cut-offs when used alone.

Kaukinen et al.[453] performed a study partially fulfilling the above requirements. Ten patients with suspected CD but only Marsh I or II lesions were compared with 27 biopsy-normal controls. The suspected cases were assessed before and after a GFD. The main results are presented in Table 52.

Table 52: Results of study assessing patients with suspected CD and Marsh I or II, before and after a GFD[453]

	Histology	EMA+	TTG+	HLA DQ2	γδ+ IELs
Initially	Marsh III – 2 (patchy) Marsh II – 7 Marsh I – 1	8/10	9/10	9/9	Marsh III – 25 cells/mm Marsh I-II – 13 Controls – 1.4
After GFD	All Marsh II re-biopsied Marsh I – 2 Marsh 0 – 5	0/10	1/10 (Slightly elevated)	Same	Reported as decreased values not reported.

Although this is a small study with possible selection bias, the authors demonstrate that in a subset of patients suspected of having CD but without villous abnormalities, CD was diagnosed in all on the basis of a response to a GFD. Raised levels γδ+ IELs, positive serology, and HLA DQ2 positivity, supported the diagnosis of CD. Patients with CD and Marsh I-II lesions had significantly higher levels of IELs than controls. Unfortunately, this study did not include a larger sample of patients with Marsh I-II histology that included serology-negative subjects. Although it is clear based on this study that CD can exist in patients with Marsh I-II lesions with raised γδ+ IELs, it is difficult to generalize these results to an unselected sample of suspected CD patients.

In a somewhat complicated but important study, Kuakinen et al.[98] assessed 271 patients with suspected CD by biopsy. Forty-five patients were classified as having definite CD on the basis of a Marsh III lesion. While in 136 patients, CD was excluded on the basis of a Marsh 0 lesion and normal levels of γδ+ IELs. The remaining 76 patients had an uncertain diagnosis of CD based on biopsy (absence of villous atrophy) and underwent HLA DQ2 and DQ8 testing. In 59 of these patients, there were minor mucosal lesions or positive serological markers, while 17 were already on a GFD prior to biopsy. CD was excluded in 11 of these 17 patients on a GFD. Of the remaining 59 patients, CD was excluded in 22 because of a negative HLA DQ2/8 given the high NPV of this test, whereas 37 were DQ2/8 positive and remained with the suspicion of CD. Overall, CD was excluded in 33 of 76 patients. Among patients suspected of CD, but without villous atrophy, Marsh I-II lesions were found in 20 DQ2/8-positive patients versus in five DQ2/8-negative patients. Elevated levels of γδ+ IELs were found in 20 patients who were DQ2/8 positive compared with seven patients who were DQ2/8 negative, and IgA-EMA was found in 16 patients who were DQ2/8 positive compared with 0 patients who were DQ2/8 negative. Although data is not provided for some patients, one can estimate the sensitivity of