Celiac dissease: Review of immunology, diagnosis and epidemiology

D.ssa Renata Auricchio,
University Federico II, Naples, Italy

Aims

Celiac disease in the 2000s: what's new?

New Diagnostic criteria and their criticisms.

Potential celiac disease: a model to study celiac disease pathogenesis

Is possible to prevent CD?

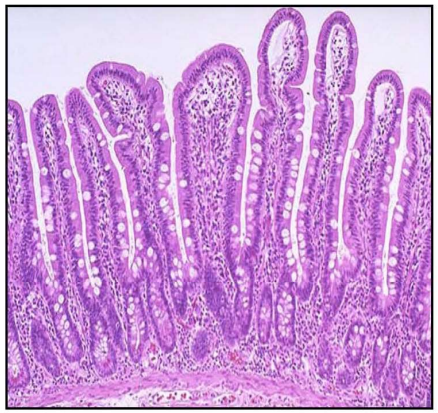
Celiac disease

- Coeliac disease is a lifelong intolerance to wheat gluten and related prolamines in rye and barley, resulting in intestinal lesion.

- It has become a common health problem in Western countries and most developing countries.

- The clinical picture is pleiomorphic and most cases go undiagnosed.

Celiac Disease
Interplay between genetic and environmental factors

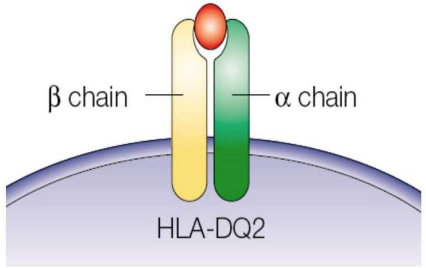


Normal intestine

Gluten proteins
(in wheat, rye, barley)

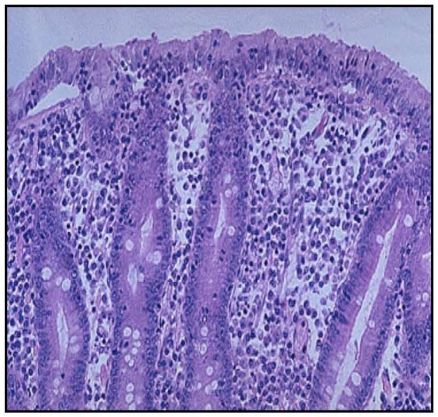
Environmental factors

Genetic factors



\+

Gene 1
Gene 2
....
Gene n



Celiac disease

HLA-DQ2 gene
on 6p21: ~40%

Prevalence of CD:
wheat consumption

Fig. 1. World map of level of wheat consumption (g/person/day).
Data from the Food and Agriculture Organization of the United Nations database (http://www.fao.org).

Lionetti E, Best PractClin Gastr 2015;29:365-379

Prevalence of CD:
frequency of HLA DQ2

Fig. 2. World map of frequency of HLA-DQ2 (%).
Data from the allelefrequencies.net database [12].

Lionetti E, Best PractClin Gastr 2015;29:365-379

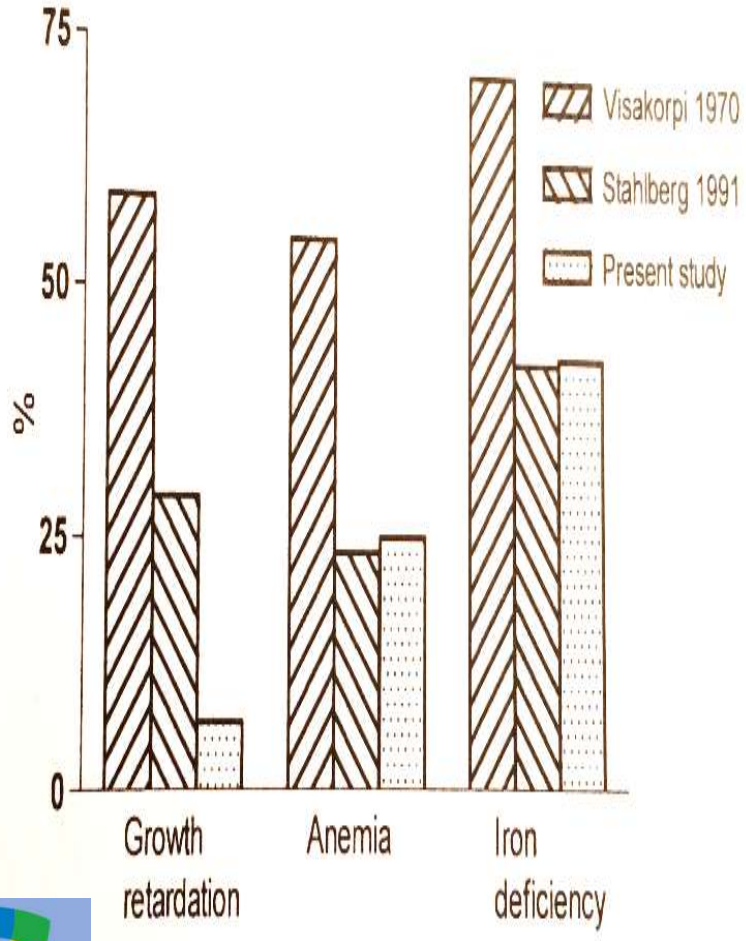
Prevalence of CD

Fig. 5. World map of celiac disease prevalence (%).
Data from studies based on the screening of unselected samples [11,17–48]. Studies on blood donors were excluded because they differed from the general population in social, health-related, and gender variables.

E. Lionetti et al. / Best Practice & Research Clinical Gastroenterology 29 (2015) 365–379

Lionetti E, Best PractClin Gastr 2015;29:365-379

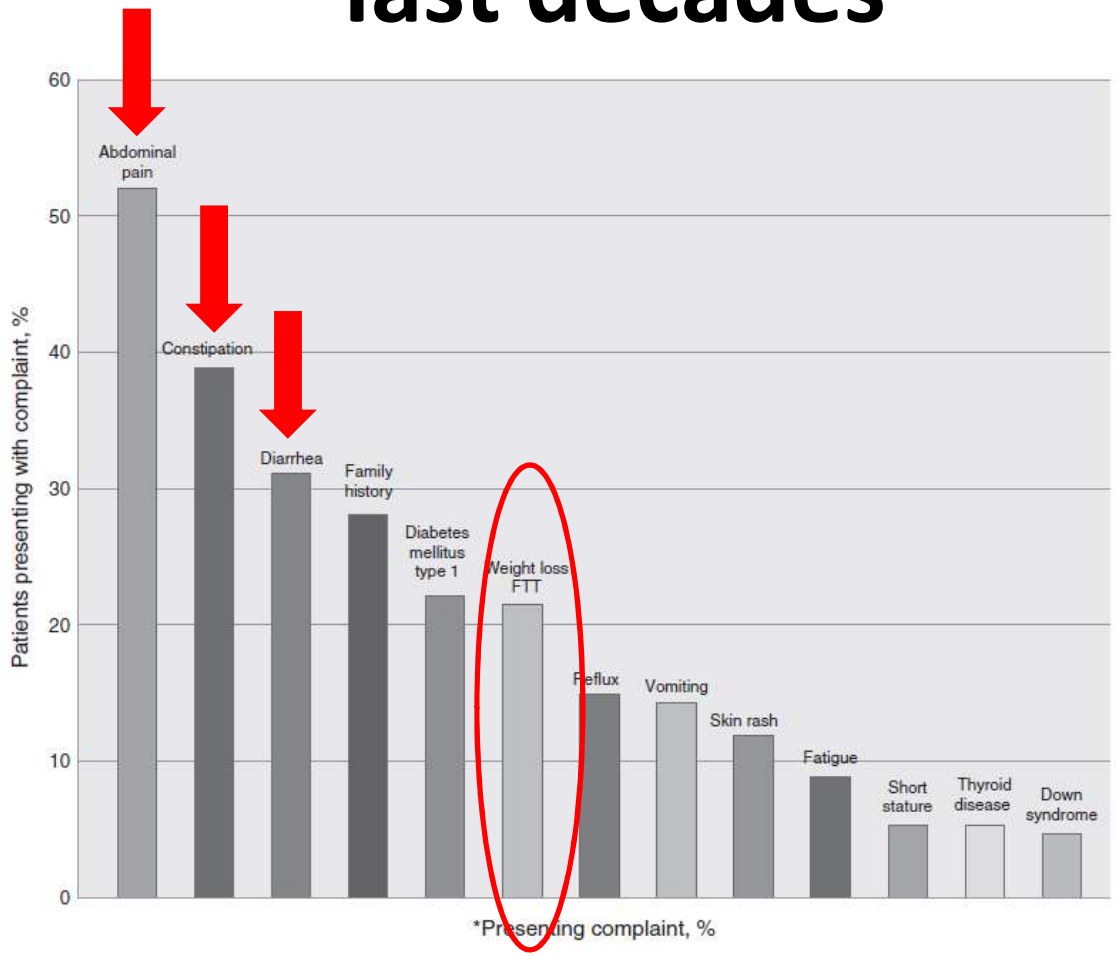
Changing clinical features of CD in the last decades



Diarrhea in the youngest (<3 y), abdominal pian in the oldest. Less frequent than previous cohort failure to thrive and iron deficiency anemia.

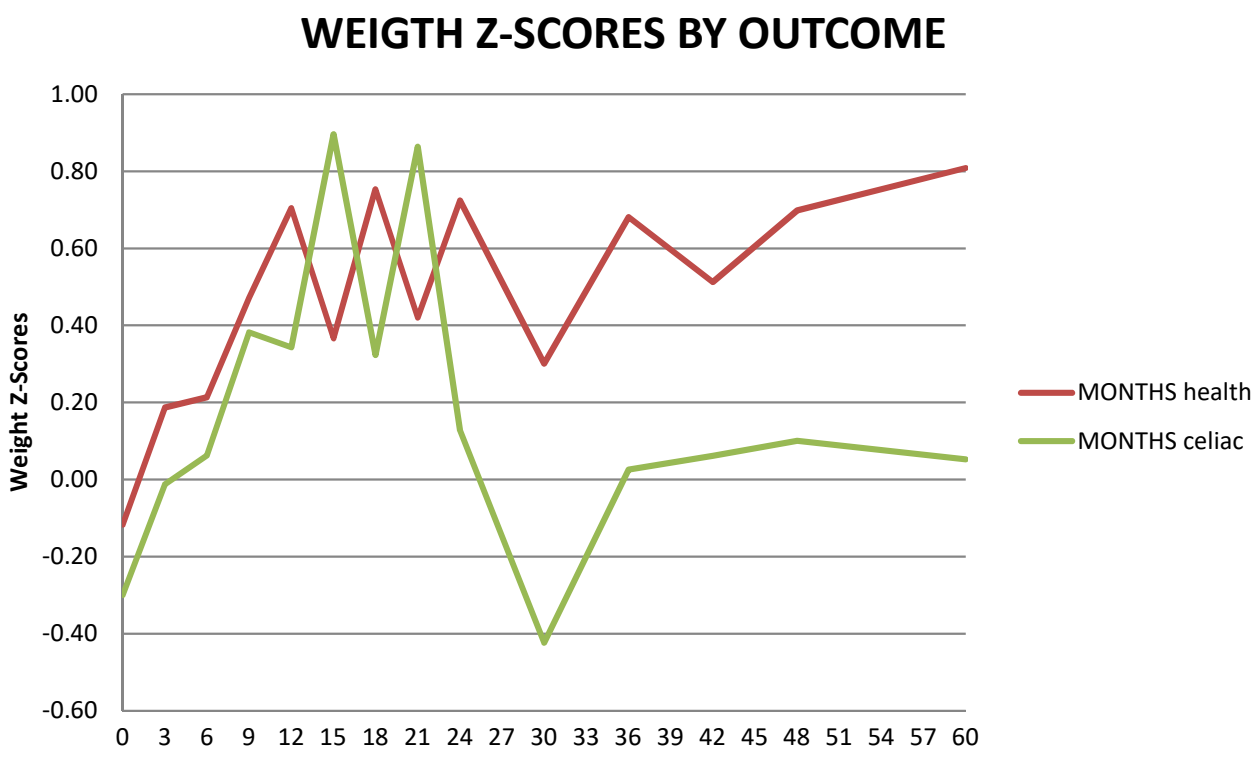
Savilahti E, Acta Ped 2010;99:1026

Changing clinical features of CDin the last decades



CD patients in NY have adbominal pain and costipation and they are older (mean age 10,7 ± 4,3 y)

Khatib M, JPGN 2016;62 (1):60-63



Reduction of **weight velocity** could predict CD diagnosis before any other clinical and serological markers in at risk children

Unpublished data

Intestinal immune events may contribute to symptoms and complications

• Through production of cytokines and other inflammatory mediators (fatigue, weight loss, increased bone turnover)

•Favouring autoimmunity (increased intestinal permeability, enhaancing mechanisms leading to induction of autoantibodies)

•Inducing local intestinal complications (e.g. lymphomagenic activity of IL15)

New Diagnostic criteria and their criticisms.

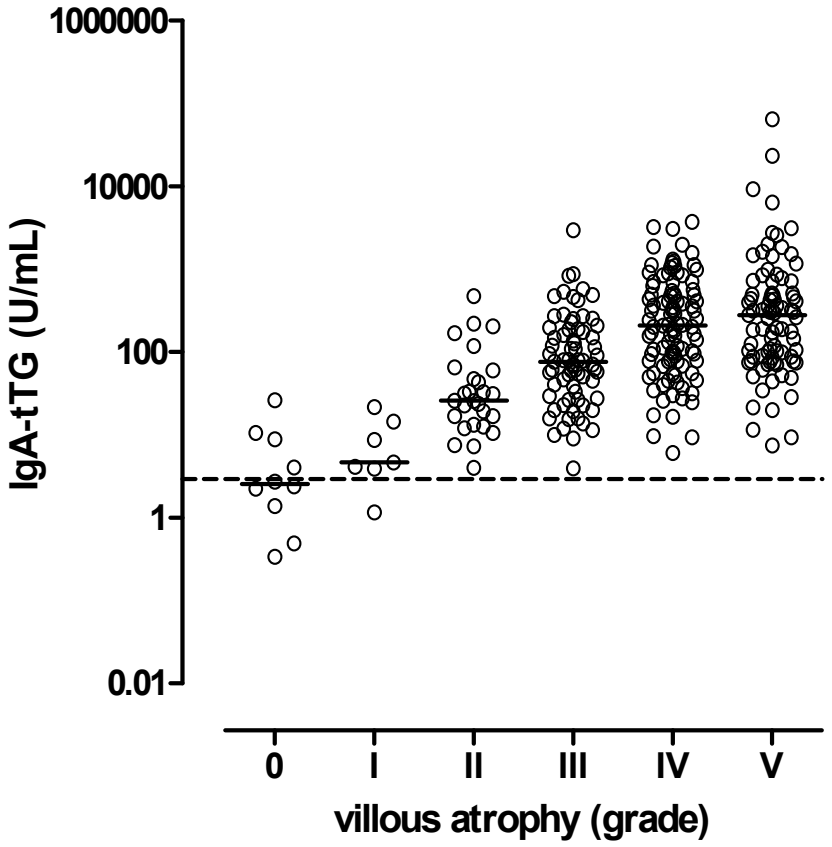
CLINICAL GUIDELINE

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease

*S. Husby, †S. Koletzko, ‡I.R. Korponay-Szabó, §M.L. Mearin, ||A. Phillips, ¶R. Shamir, #R. Troncone, **K. Giersiepen, ††D. Branski, ‡‡C. Catassi, §§M. Lelgeman, ||||M. Mäki, ¶¶C. Ribes-Koninckx, ###A. Ventura, and ****K.P. Zimmer, for the ESPGHAN Working Group on Coeliac Disease Diagnosis, on behalf of the ESPGHAN Gastroenterology Committee*

JPGN 2012; 54: 136-16

High serum anti-TG2 antibodies correlation with histology lesions in children



Dahlbom et al. JPGN, 2009

Table 1. The positive predictive value (PPV) for different cut-offs of IgA-tissue transglutaminase antibody (TGA) levels in 146 patients

TGA* cut-off		No. patients		
		Coeliac	Not coeliac	
U/mL				PV (%)
10				95
20				98
30	10	91	0	100
50	16.7	68	0	100
>100	>33	34	0	100

> 10 x upper limit of normal (ULN)

* TGA is expressed as U/mL and as multiples of the upper limit of normal (ULN).

Hill, Aliment Pharm Ther 2008

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:166–171

Degree of Damage to the Small Bowel and Serum Antibody Titers Correlate With Clinical Presentation of Patients With Celiac Disease

JUHA TAAVELA,* KALLE KURPPA,* PEKKA COLLIN,‡,§ MARJA-LEENA LÄHDEAHO,* TEEA SALMI,§,‖ PÄIVI SAAVALAINEN,¶ KATRI HAIMILA,# HEINI HUHTALA,** KAIJA LAURILA,* HARRI SIEVÄNEN,‡‡ MARKKU MÄKI,* and KATRI KAUKINEN‡,§

Results: The ratio of the villous height to crypt depth correlated with the severity of gastrointestinal symptoms, quality-of-life scores, laboratory test results, nummers of intraepithelial CD3+ cells, and serum levels of antibodies associated with celiac disease

Biopsy: recommendations

Histological assessment may be omitted in:

- Symptomatic cases
- With high IgA anti-TG2 levels, (10 x upper normal limits)
- Verified by EMA positivity
- HLA DQ2 and/or DQ8 heterodimer positive

Follow up should include significant symptomatic improvement as well as normalization of coeliac antibody tests.

Critical issues

What we mean for symptomatic children?

Anti TG2 kits performances are different
Should cut offs limits be validated locally?
Is it necessary an international standard for antiTG2 antibodies?
EMA are really necessary?

HLA typing really adds to serology in those with anti-TG2 >10xULN

How many false positive we have using the new criteria?

	Total	ESPGHAN criteria + ve	Villous atrophy
Donat (JPGN 2015)	751	336	336 (100)
Klapp (JPGN 2013)	50	116	116 (100)
Guandalini (JPGN 2013)	279	115	115 (100)
Gidrewicz (Am J Gastroenterol 2015)	775	263	256 (97)

Main aims for PED gi in CD are:

- Management of Potential CD children
- Prevention of CD

Potential coeliac disease

Presence of CD-specific antibodies and compatible HLA, but without histological abnormalities in duodenal biopsies. May or may not have symptoms and signs. May not develop a gluten-dependent enteropathy later

(Husby et al, 2012)

Questions

1. Which are the **clinical and laboratory features** of potential CD?

2. Are these features different **in Marsh 0** vs **Marsh 1** potential CD?

3. Which is the **natural history** of this condition?

Questions

Should it be treated by **GFD?**

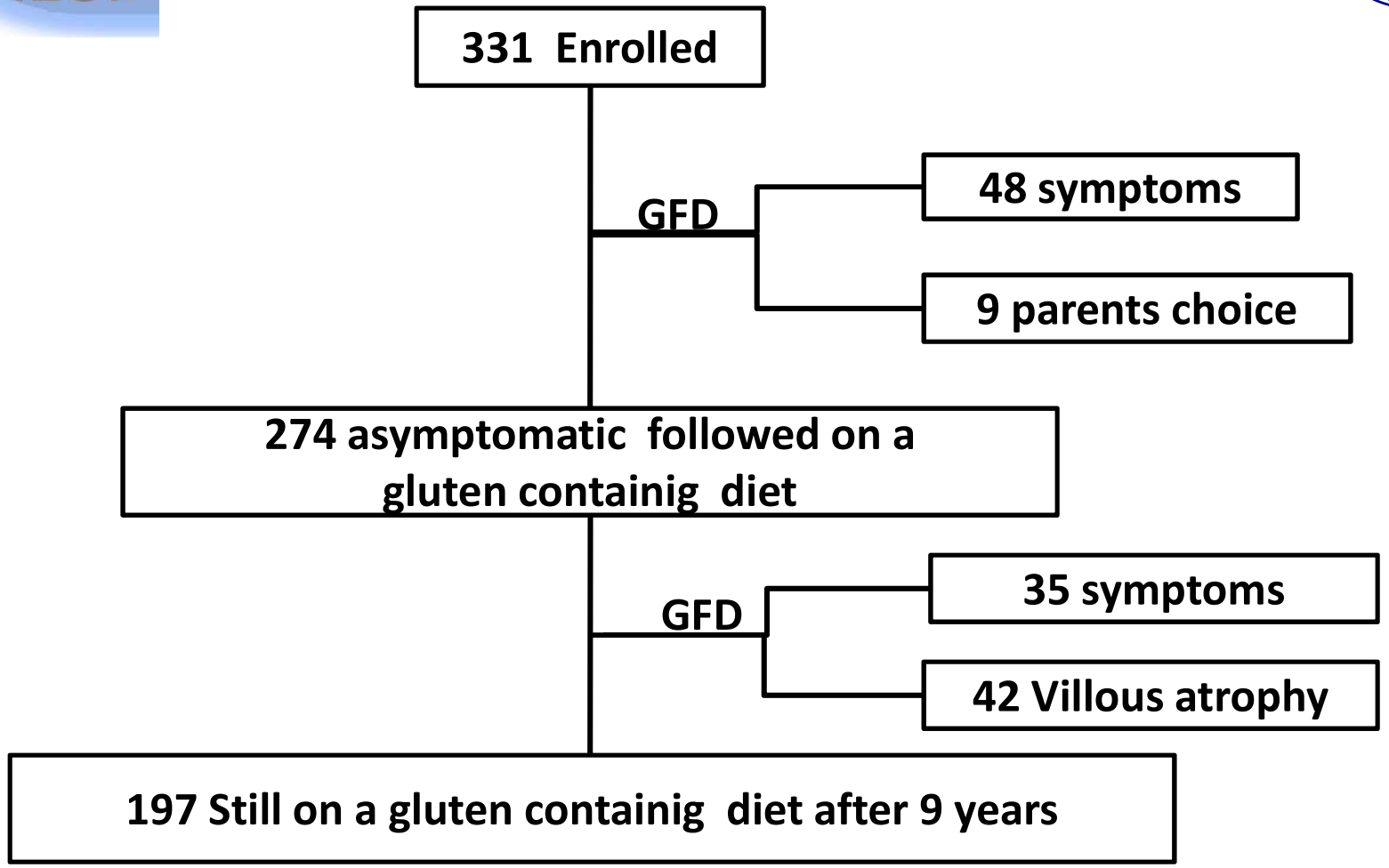
Decision should be based on:

- Documented benefit from GFD or demonstration of increased risk of complications on normal diet

Randomisation protocol!

- More precise data about long term evolution (percentage of patients evolving to villous atrophy)

Potential Celiac Disease Progression of the study cohort



Potential Celiac Disease
Clinical, histological and serological features (331 patients)

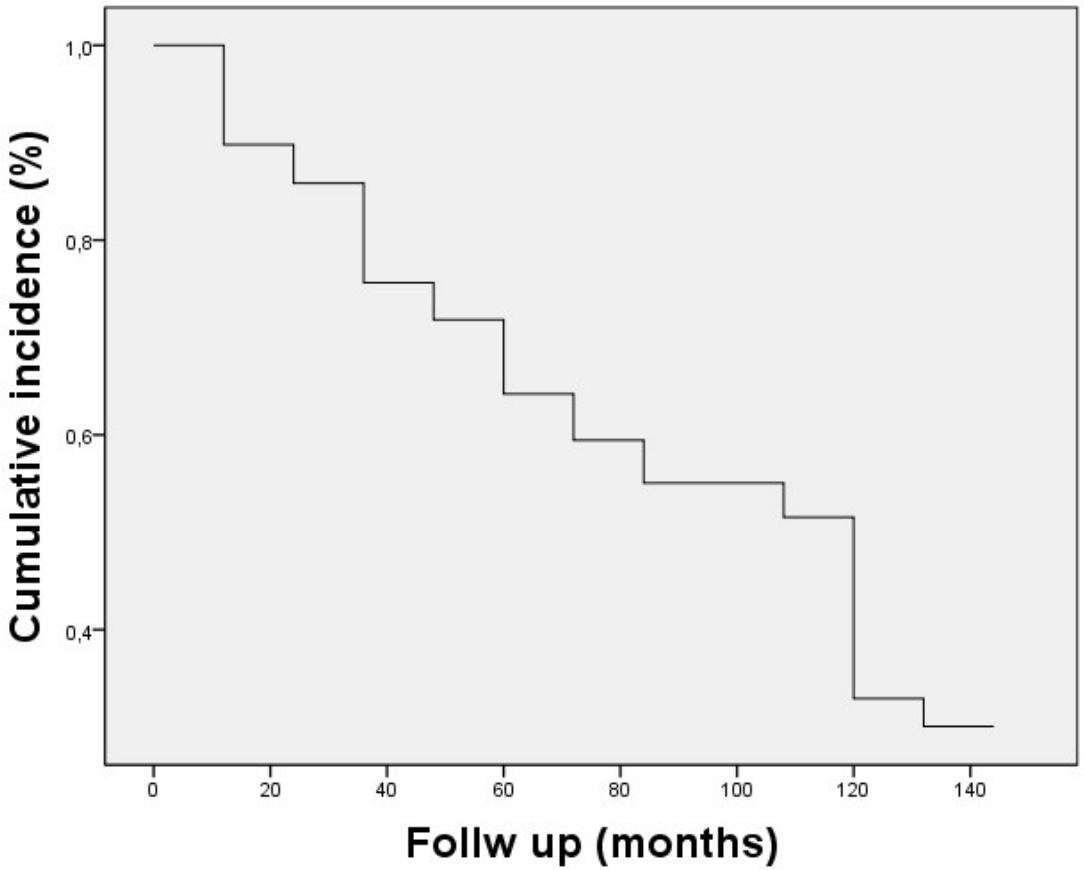
- 14,6% of patients with CD diagnosis 2001-2016
- Age: 6,3 years (range: 1.1-17,84),
- 222 girls (67,1%)
- Clinical: 48 symptomatic (14,5%), 123 (37,1%) at-risk groups (50 autoimmune, 73 first degree relatives)
- Histology: 34,4 % Marsh 0, 61,3%Marsh 1
- Anti-TG2 median titer: 28,99 U/l (vn. <7).
- Diet: normal daily gluten intake

Trend of serological marker during the follow up

Anti-TG2 variations:

- Negative 32,5%
- Fluctuant 33,5%
- Persistently positive 33,9%

Will all become coeliac?



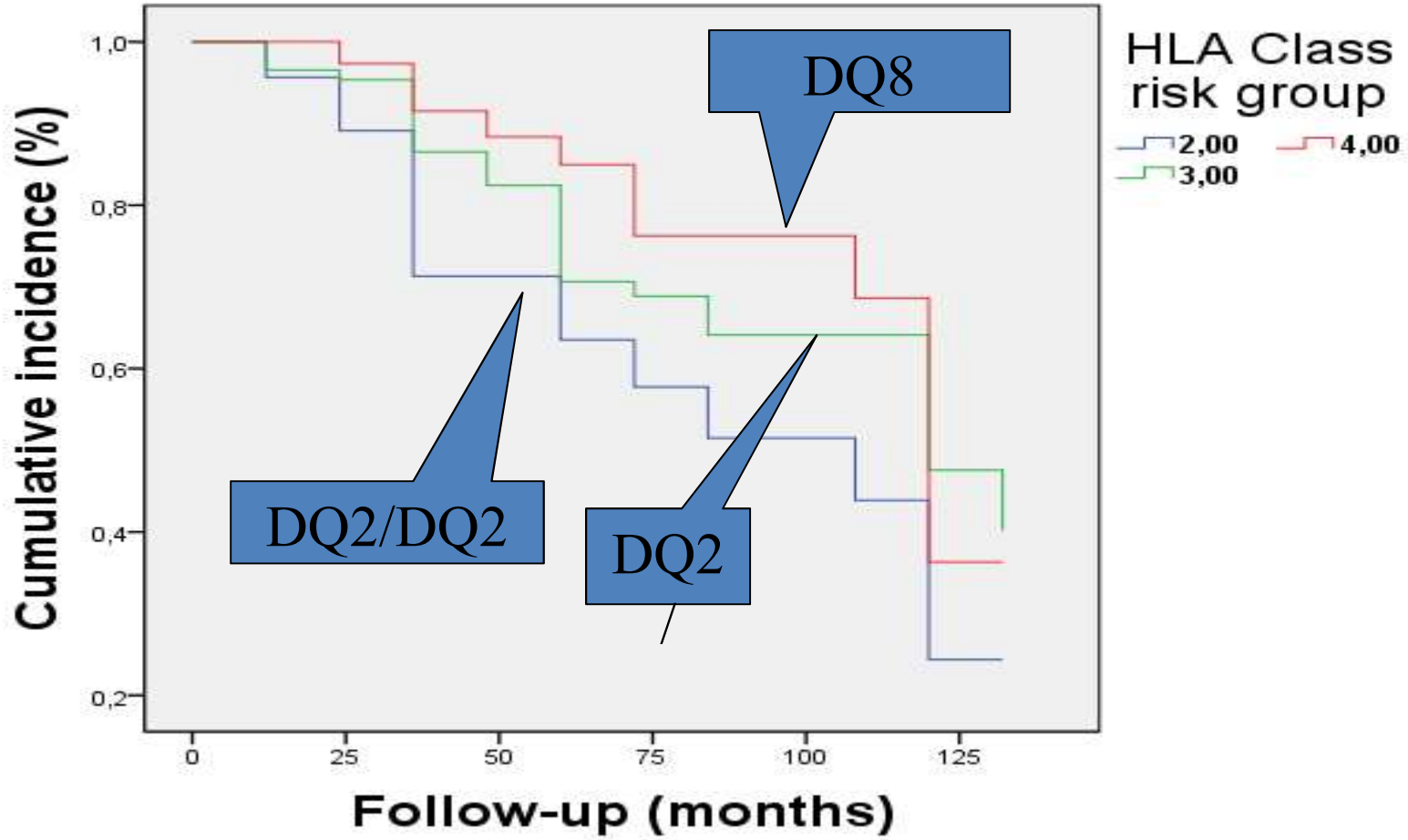
36% of probability to remain potential after 9 years of follow up on a gluten containing diet!!

Most patients (22/42) evolved in celiacs in the first two years of follow up on a GCD.

Biomarkers at time 0 and development of villous atrophy

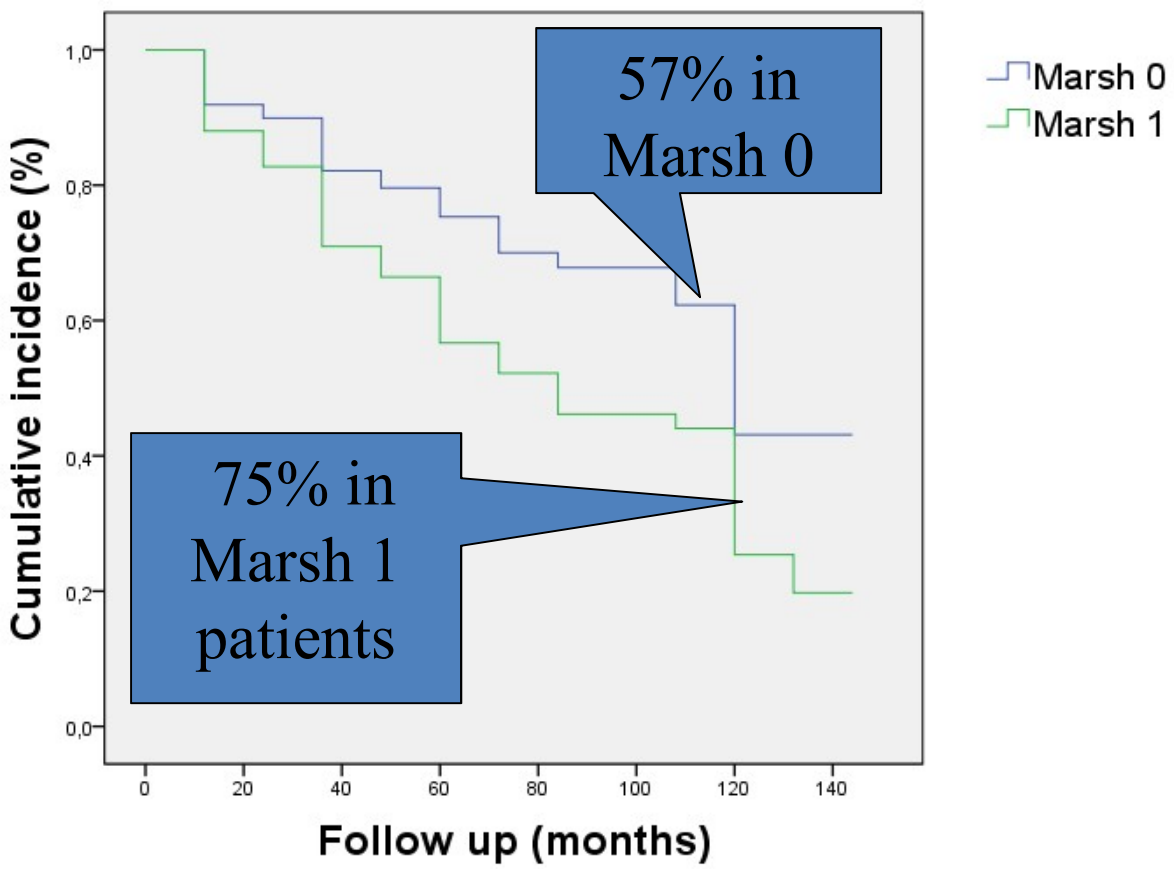
	Remained "Potential"	Evolved to Fully Celiac	Sig. (p)
Anti-TG2 titer	32,38	32,77	0,483
CD3	35,08	42,62	0,161
γδ	**6,89**	**10,86**	**0,000**
CD25	**8,59**	**11,17**	**0,000**
Presence of anti-TG2 intestinal deposits	**58,3%**	**77,9%**	**0,004**

Will all become coeliac?



All have at risk HLA, but still there is a dose-effect p = 0,04

Will all become coeliac?



Major risk to became celiac depend on Marsh grade at time biopsy (p= .009)

Conclusions

"Potential" Coeliac Disease is increasingly diagnosed

Most are (apparently) asymptomatic

With a follow-up up to 9 years, 64 % progress to villous atrophy; most in the first 2 years of follow up

Risk factors are

- High genetic risk (HLA)
- Persistence of raised levels of anti-tTG2
- Infiltrative lesion (Marsh 1)

Prevention of CD: what could we do in the 2016?

- ✓ Genetic risk determination

- ✓ Preventing strategies

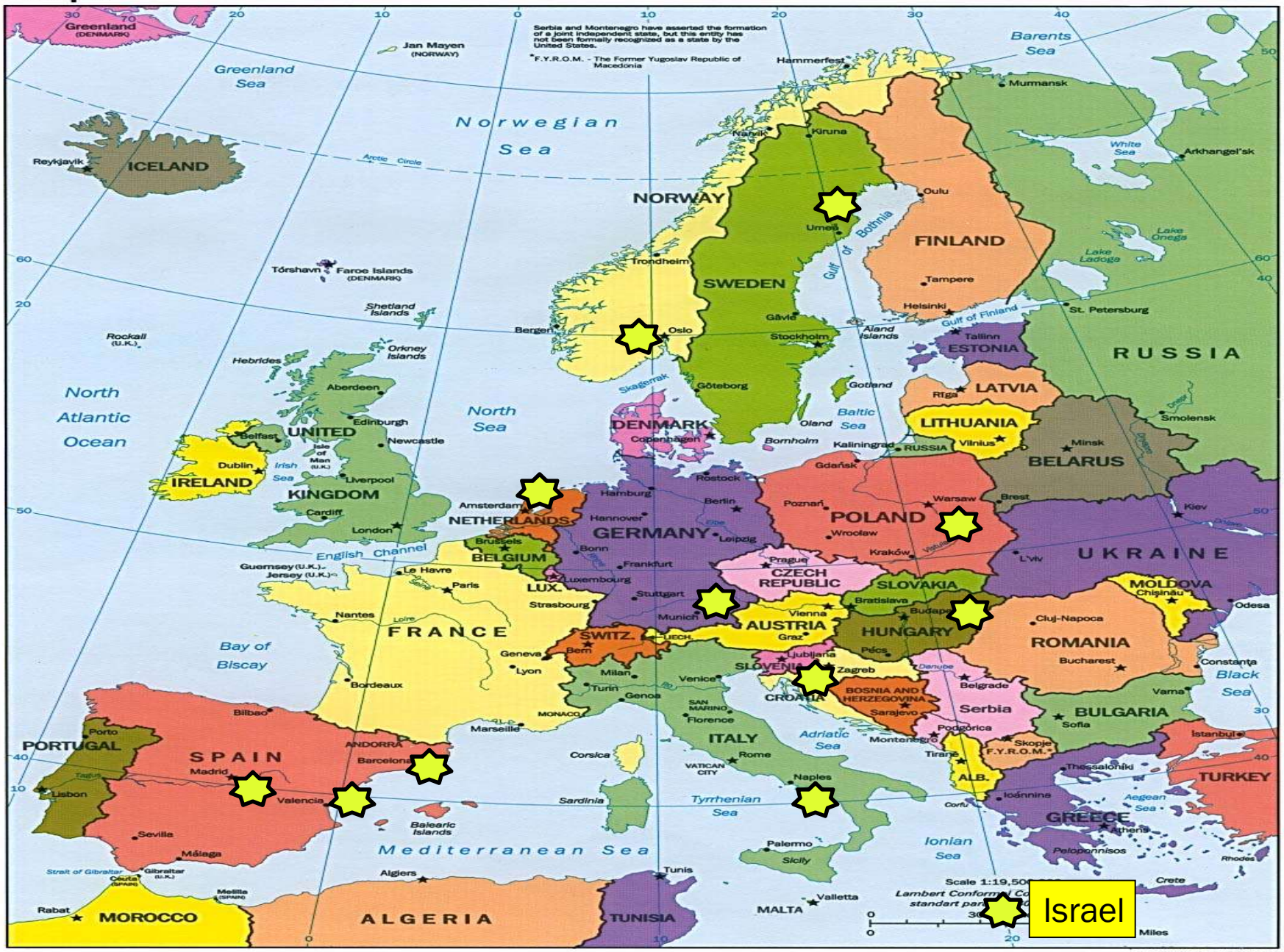
(time and quantity of gluten during weaning, breastfeeding, less immunoreactive wheat-monococcus)

Prevent CD- EUFP6

Influence of infant nutrition on the risk of developing coeliac disease (CD)

Hogen Esch CE. Eur J Gastroenterol Hepatol. 2010

Europe



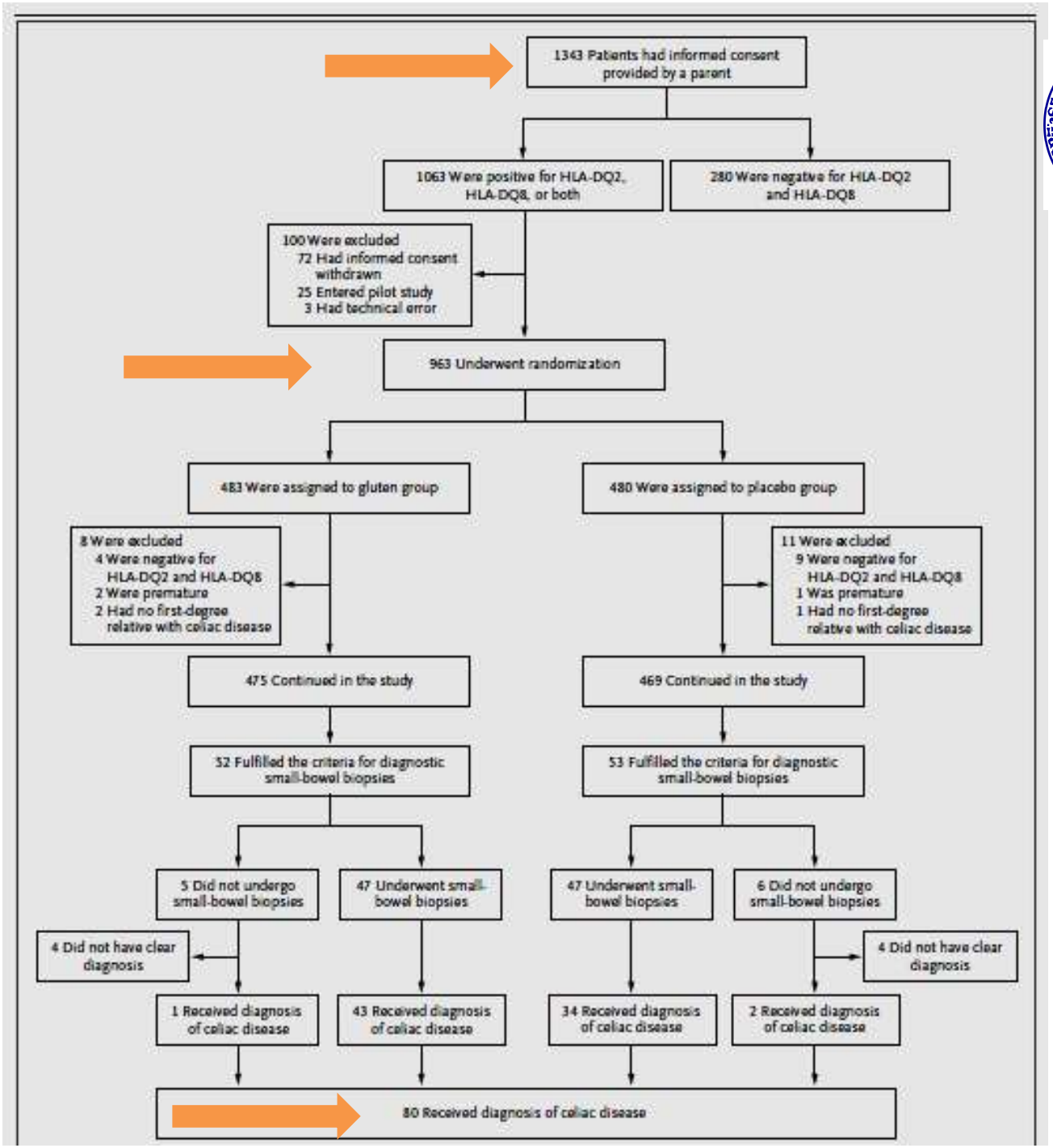
The NEW ENGLAND JOURNAL of MEDICINE

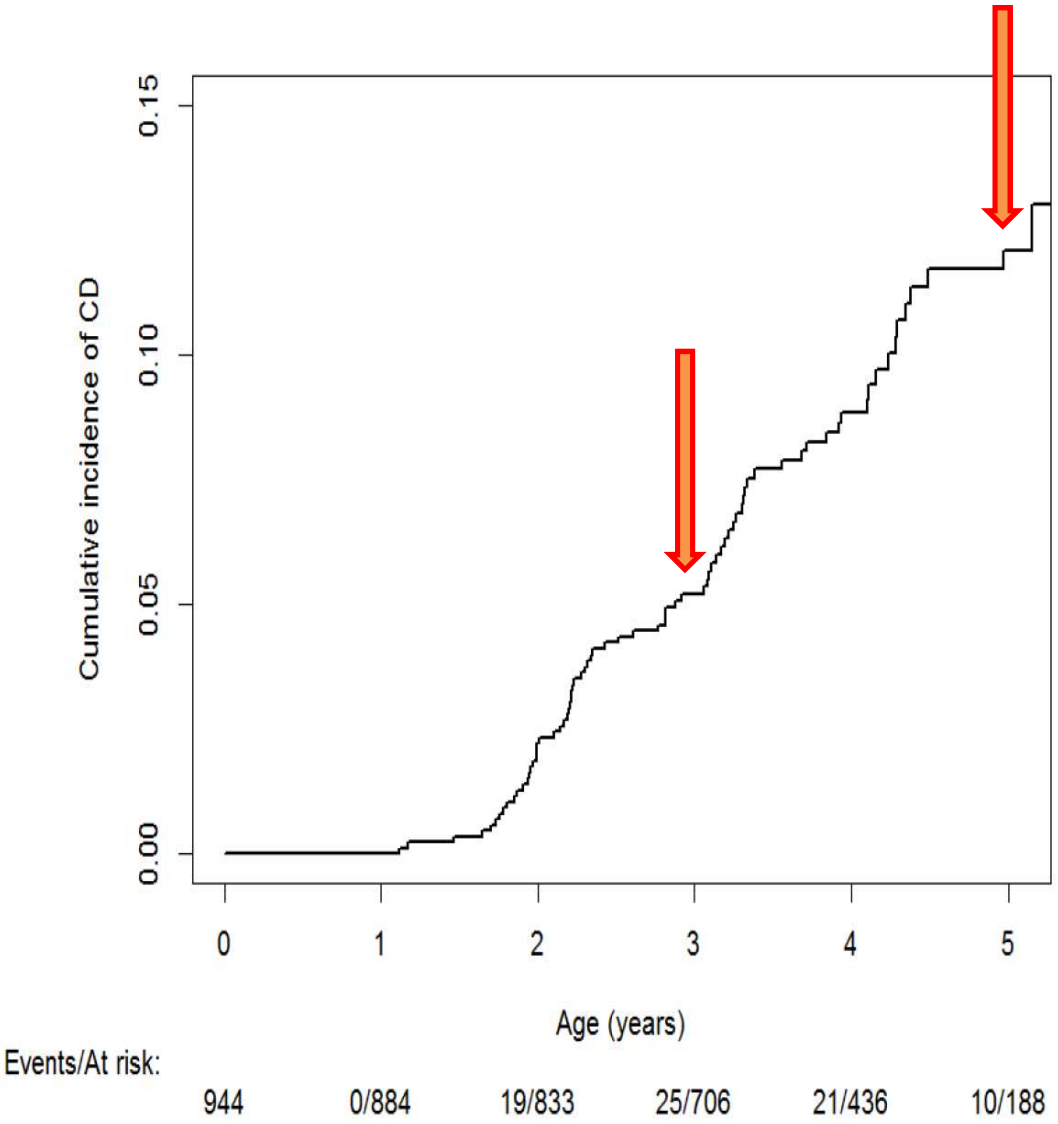
ORIGINAL ARTICLE

Randomized Feeding Intervention in Infants at High Risk for Celiac Disease

S.L. Vriezinga, R. Auricchio, E. Bravi, G. Castillejo, A. Chmielewska, P. Crespo Escobar, S. Kolaček, S. Koletzko, I.R. Korponay-Szabo, E. Mummert, I. Polanco, H. Putter, C. Ribes-Koninckx, R. Shamir, H. Szajewska, K. Werkstetter, L. Greco, J. Gyimesi, C. Hartman, C. Hogen Esch, E. Hopman, A. Ivarsson, T. Koltai, F. Koning, E. Martinez-Ojinaga, C. te Marvelde, A. Mocic Pavic, J. Romanos, E. Stoopman, V. Villanacci, C. Wijmenga, R. Troncone, and M.L. Mearin

N Engl j Med 2014; 371; 1304-15

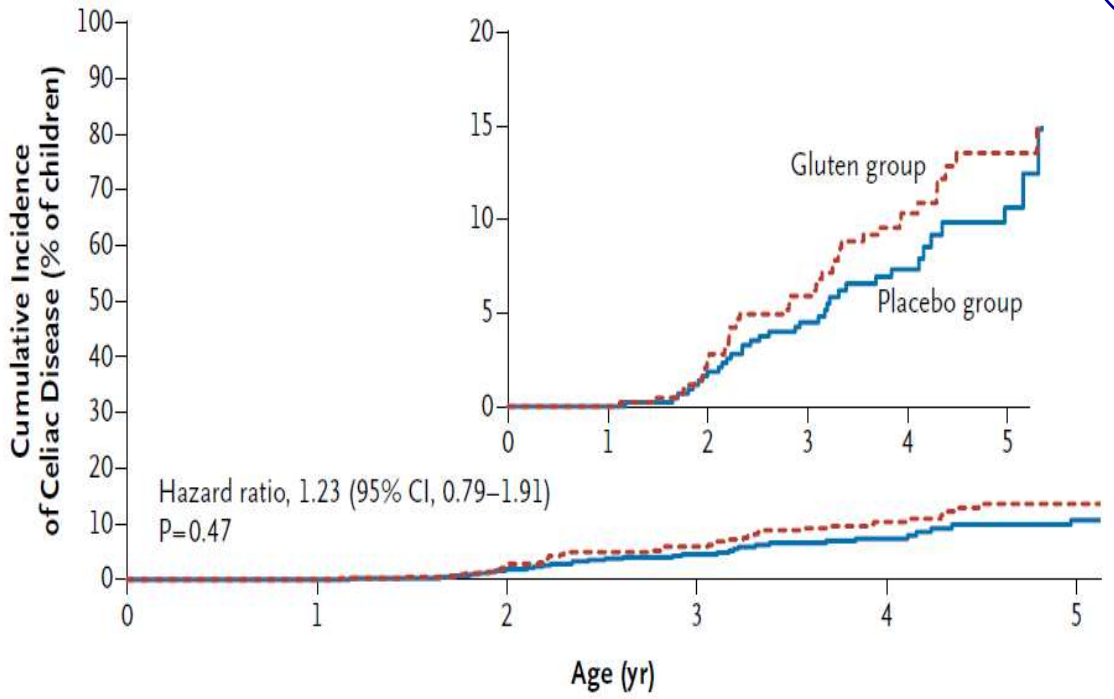

1343 Patients had informed consent provided by a parent
1063 Were positive for HLA-DQ2, HLA-DQ8, or both
280 Were negative for HLA-DQ2 and HLA-DQ8
100 Were excluded
72 Had informed consent withdrawn
25 Entered pilot study
3 Had technical error
963 Underwent randomization
483 Were assigned to gluten group
480 Were assigned to placebo group
8 Were excluded
4 Were negative for HLA-DQ2 and HLA-DQ8
2 Were premature
2 Had no first-degree relative with celiac disease
11 Were excluded
9 Were negative for HLA-DQ2 and HLA-DQ8
1 Was premature
1 Had no first-degree relative with celiac disease
475 Continued in the study
469 Continued in the study
52 Fulfilled the criteria for diagnostic small-bowel biopsies
53 Fulfilled the criteria for diagnostic small-bowel biopsies
5 Did not undergo small-bowel biopsies
47 Underwent small-bowel biopsies
47 Underwent small-bowel biopsies
6 Did not undergo small-bowel biopsies
4 Did not have clear diagnosis
4 Did not have clear diagnosis
1 Received diagnosis of celiac disease
43 Received diagnosis of celiac disease
34 Received diagnosis of celiac disease
2 Received diagnosis of celiac disease
80 Received diagnosis of celiac disease



Cumulative incidence: 6% at 3 years

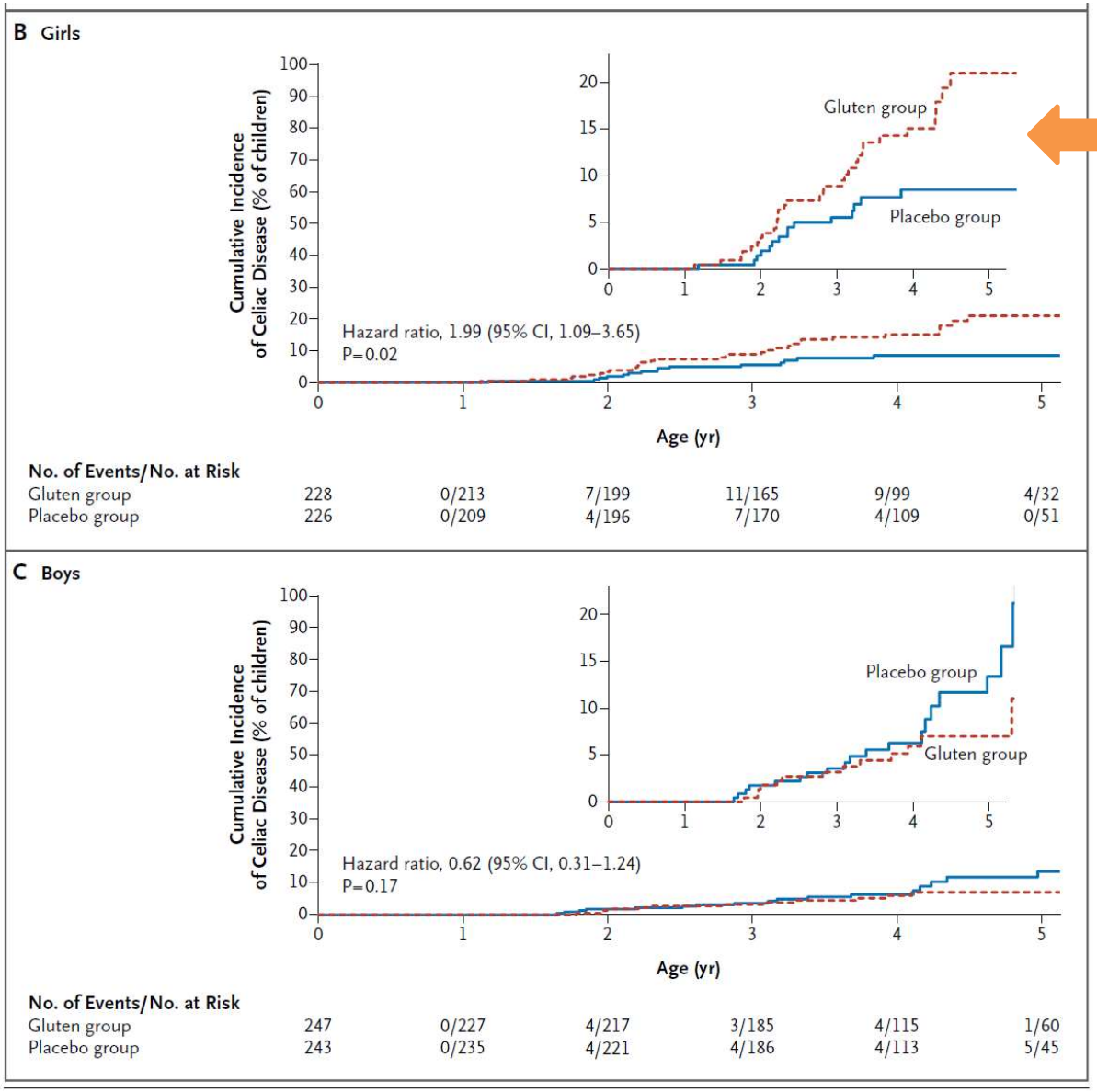
13.5% at 5 years

ll Children

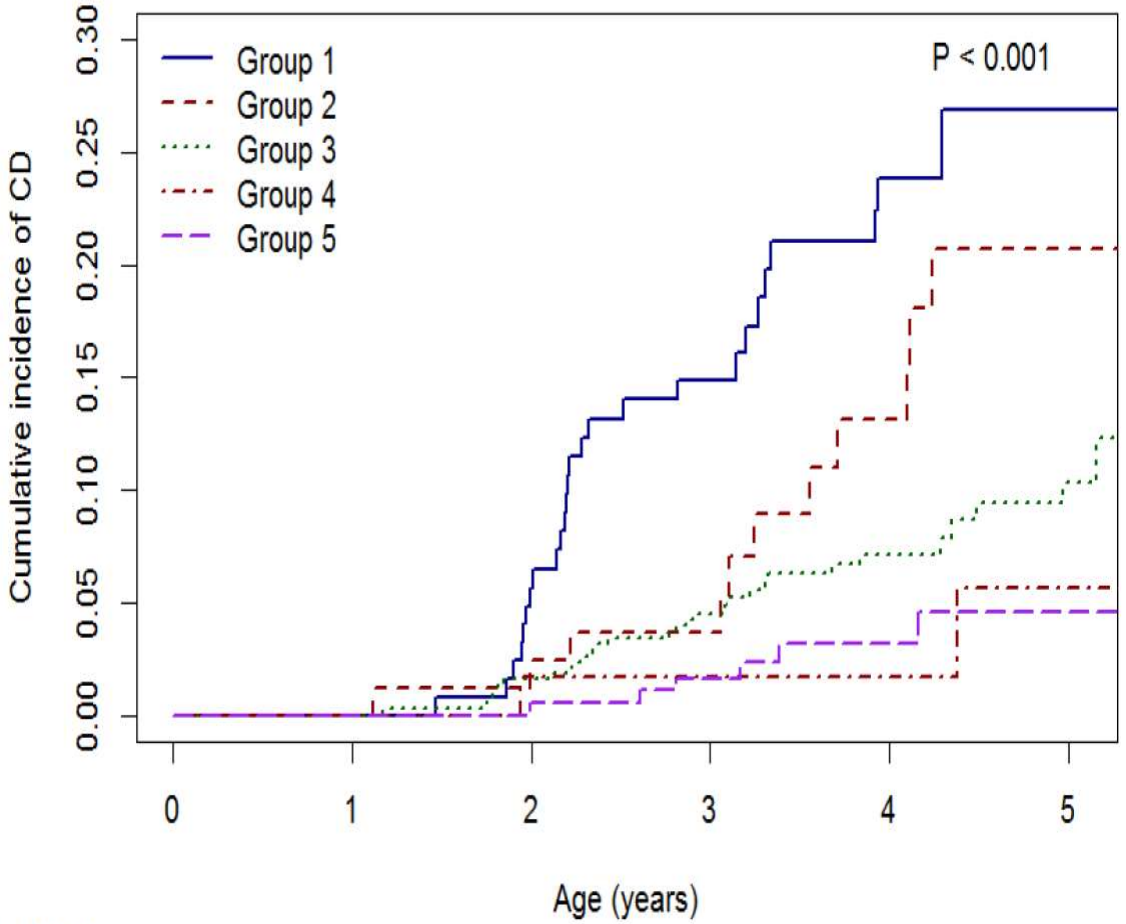


No. of Events/No. at Risk						
Gluten group	475	0/440	11/416	14/350	13/214	5/92
Placebo group	469	0/444	8/417	11/356	8/222	5/96

No statistically significant differences were observed between gluten and placebo group



Females showed an increased risk to develop CD either at 3 years (8.9 vs 3.2%) and at 5 years (15.1 vs 5.9%) compared to males



Events/At risk						
Group 1:	129	0/127	7/114	11/92	7/49	1/18
Group 2:	88	0/85	2/79	1/69	5/40	3/22
Group 3:	417	0/388	6/373	11/313	7/205	4/85
Group 4:	66	0/60	1/57	0/48	0/34	1/16
Group 5:	211	0/195	1/187	2/163	2/98	1/41

More at risk children homozygous for DQ2 (HLA class 1 risk): 14.9% at 3 years and 26.9% at 5 years.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Introduction of Gluten, HLA Status, and the Risk of Celiac Disease in Children

Lionetti E, NEJM 2014;371:1295-303

Conclusions.

- Celiac disease prevalence improves in the last decades all around the world
- New clinical and histological phenotypes are emerging.
- Validate new diagnostic criteria in the future
- Possible preventive strategies could be planned for at risk children.