What Wikipedia Can't Tell You About Celiac Disease Prevention: Hear it from the Experts

With Alessio Fasano, M.D., Carlo Catassi, M.D., and Sabine Vriezinga, M.D.

Important Reminders!

① Will this information be available at a later date?

- Yes, always!
- Webinar recording will be posted along with the webinar slides within **72 hours** after the live webinar ends at CeliacCentral.org/webinars/archive/

② Are continuing education credits available?

- Yes!
- Attendees must **complete the follow-up survey** in order to access this certificate.
  - **The follow-up survey will be sent on Thursday, April 30th through an email from NFCA.**
- To ensure that you receive this email, make sure that NFCA (National_Foundation_for_Celiac_A@gmail.vresp.com) is on your **allowed senders list**.
  - Accidentally unsubscribed? Register for the webinar with a new email address
  - Be sure your email address is spelled correctly when registering
- Continuing education credits given **for live viewers** *only*
  - We encourage you to check out our archived webinars, but note that continuing education credit will not be given
- In the case of group viewing, **only the registered and logged in participant will receive credit**

Seriously, Celiac Disease

NFCA has come up with a research-tested way of talking to your family about celiac disease testing. Introducing the *Seriously, Celiac Disease* series – watch the video, then download the Dos and Don'ts guide to help you talk to your family offline:

www.SeriouslyCeliac.org

#TalkTellTest

Learning Objectives

1) Learn about the most recent hypotheses and findings in celiac disease prevention
2) Discover what the future may hold for research on celiac disease prevention
3) Understand the importance of celiac disease prevention
4) Know your role as a patient in the advancement of the field

Welcome!

Alessio Fasano, M.D.

- Director of the Center for Celiac Research and Treatment at MassGeneral Hospital for Children (MGHfC)
- Prevalence study published in 2003 established the rate of celiac disease at 1 in 133 Americans
- Visiting Professor at Harvard Medical School
- Chief of the Division of Pediatric Gastroenterology and Nutrition at MGHfC
- Recently authored *Gluten Freedom* to dispel some of the current confusion about gluten and how it can affect your health

Welcome!

Carlo Catassi, M.D.

- Head of the Department of Pediatrics at the Università Politecnica delle Marche, Ancona, Italy
- President of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition during the years 2013-2016
- In 2001, he joined the Center for Celiac Disease (CFCR) at the University of Maryland School of Medicine, Baltimore (USA) and was appointed as Co-Director of the CFCR in 2003
- One of the first researchers to show the high prevalence of undetected celiac disease in different countries and to conceptualize the “celiac iceberg”
- Has published around 140 papers on various aspects of celiac disease and pediatric gastroenterology

Welcome!

Sabine Vriezinga, M.D.

- Completed her medical degree in 2012 at the University of Leiden, the Netherlands
- Currently a PhD-fellow in the department of pediatrics of Leiden University Medical Center
- Works for the multicenter PreventCD project (www.preventcd.com), investigating whether changing infant feeding practices can prevent celiac disease
  - In October 2014, the results of this study were published in the *New England Journal of Medicine*
- Works on the ongoing study CoelKids (www.coelkids.nl)

Can We Prevent Celiac Disease?

Opportunities and Challenges

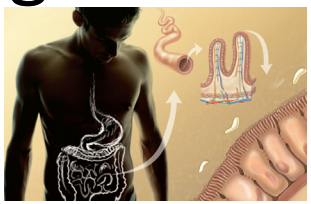
Alessio Fasano, M.D.

Mucosal Immunology and Biology Research Center

And Center for Celiac Research

Massachusetts General Hospital, Boston MA – U.S.A.

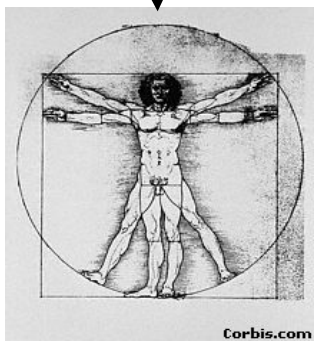
The Yin and Yang Between Tolerance and Immune Response Leading to Autoimmune Diseases



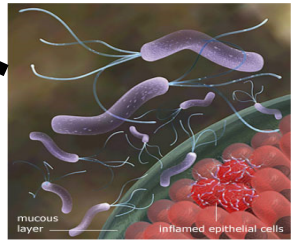
Increased Gut Permeability

Human Genome

Immune Response



Environmental Factors

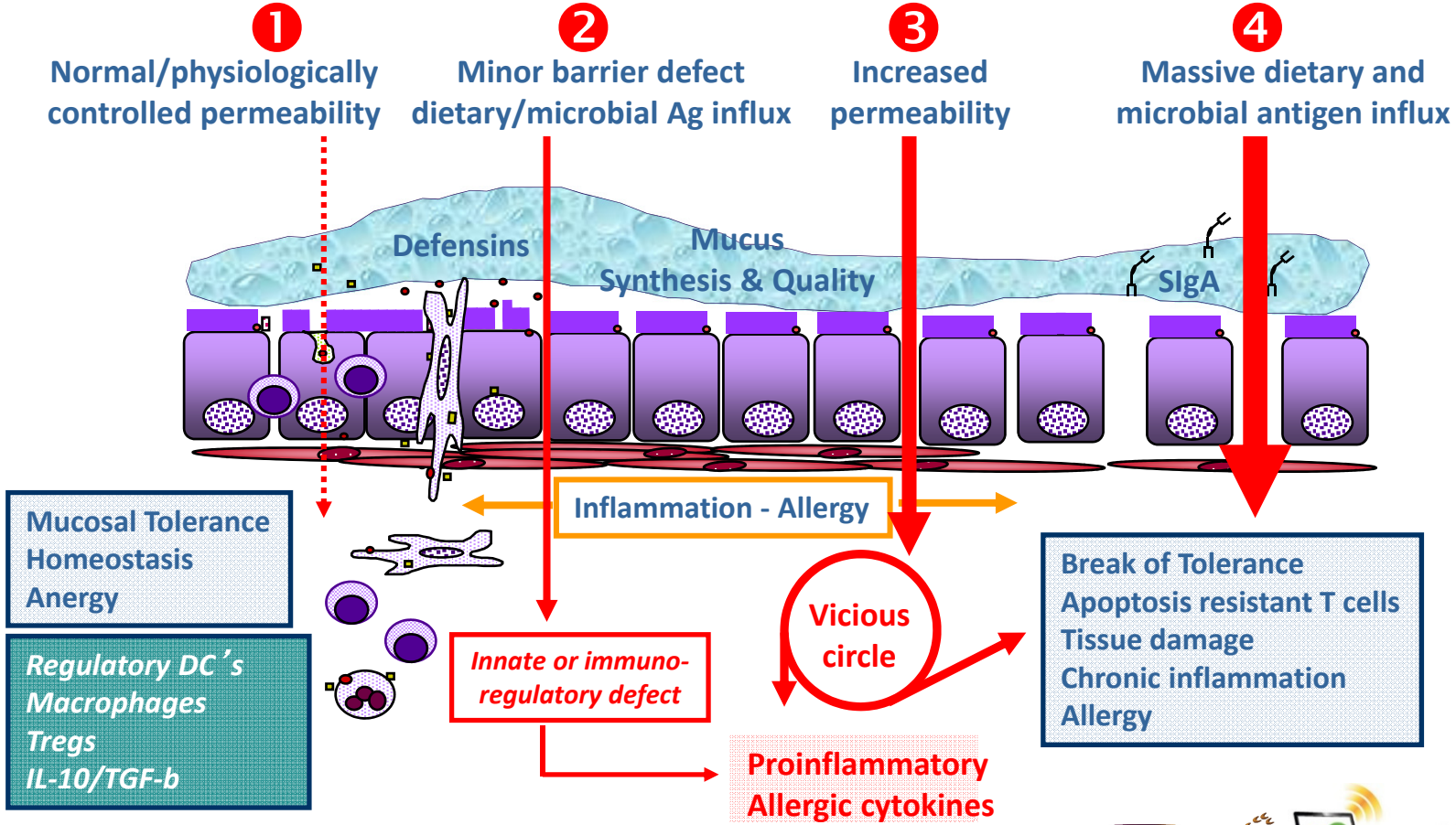


Microbiome

Clinic Outcome

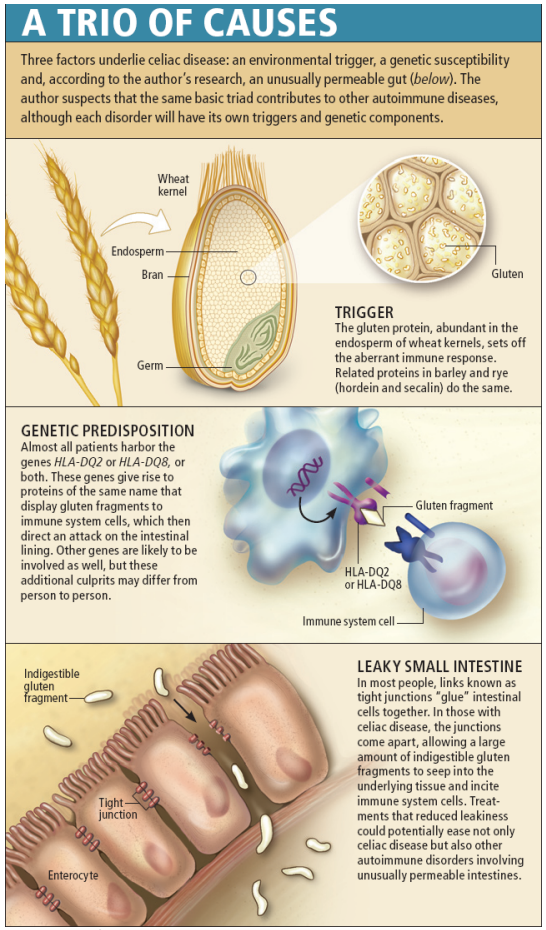
Loss of Mucosal Immune Regulation

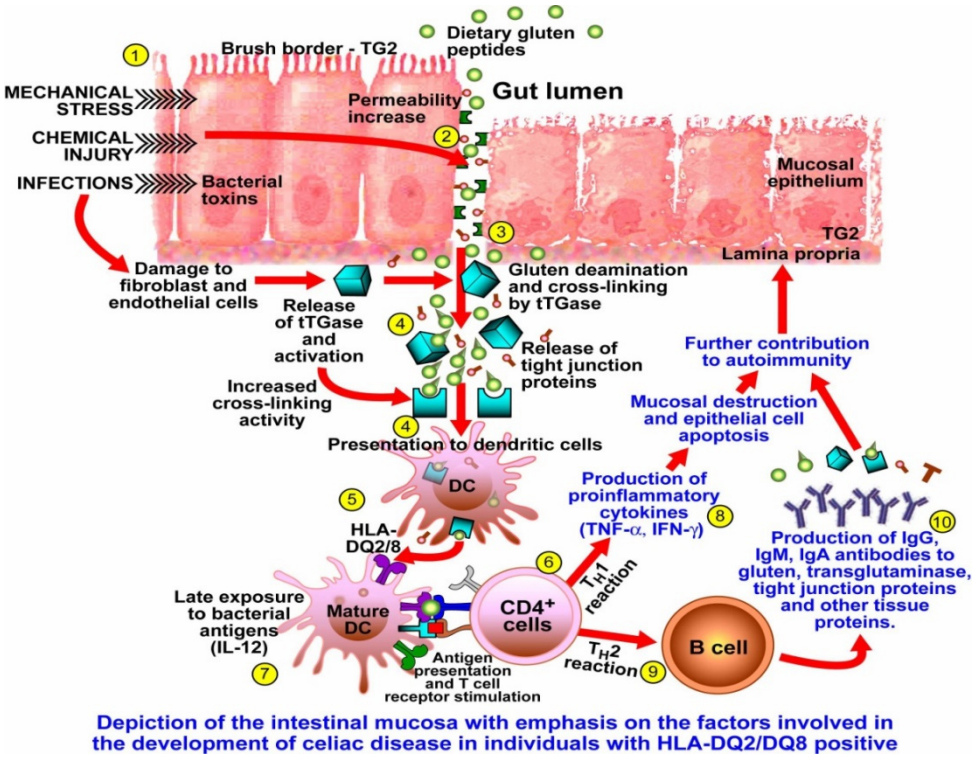
Chronic Inflammation-Allergy



Adapted from P. Brandtzaeg, Beneficial Microbes 2010

The Holy Trinity of the Autoimmune Mechanisms in Celiac Disease





Depiction of the intestinal mucosa with emphasis on the factors involved in the development of celiac disease in individuals with HLA-DQ2/DQ8 positive

Fasano A; Scientific American Aug. 2009

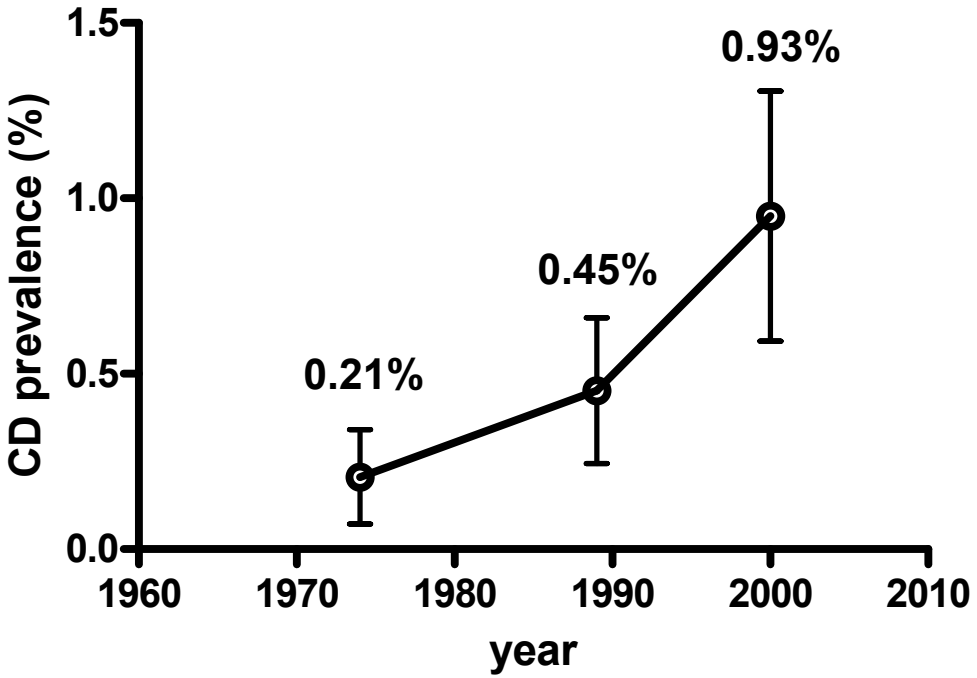
Celiac Disease as a Unique Model of Autoimmunity

- The only autoimmune disease in which specific major histocompatibility complex (MHC) class II HLA (DQ2 and/or DQ8) are present in >95% of patients
- The auto-antigen (tissue Transglutaminase) is known
- The environmental trigger (gluten) is known
- Elimination of the environmental trigger leads to a complete resolution of the autoimmune process that can be re-ignited following re-exposure to gluten

Increased Prevalence Over Time in U.S.A.

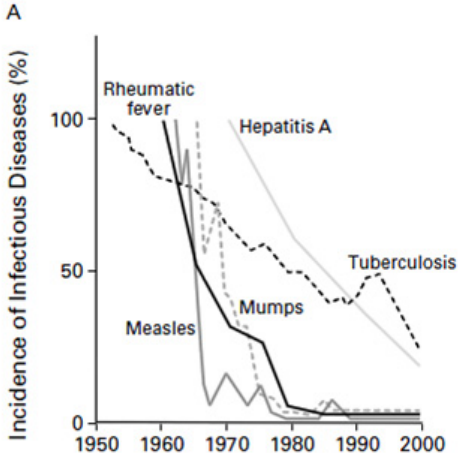
(In Line with Other Autoimmune Diseases)

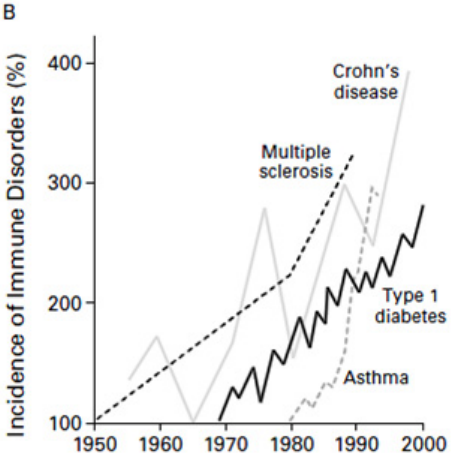
During the past 35 years the true prevalence of celiac disease in the USA doubled every 15 years



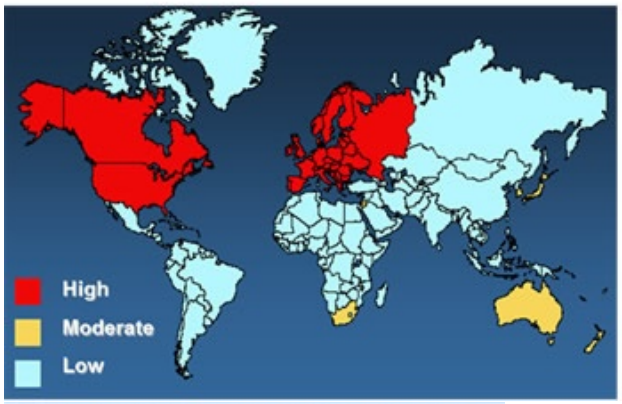
C. Catassi et al, Annal Med 2010;42:530-8.

The Hygiene Hypothesis





Autoimmune disorders incidence



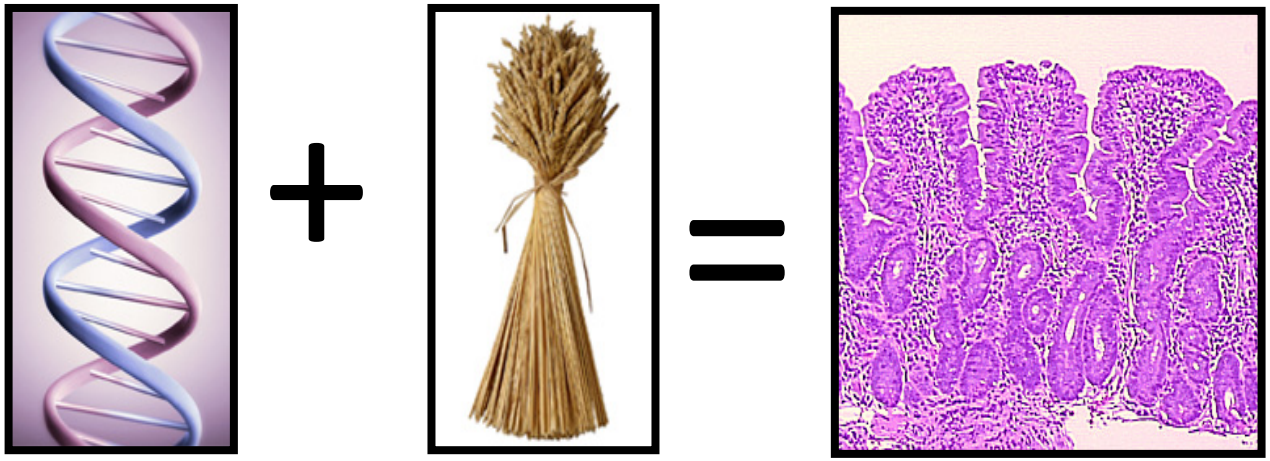
Helminths infestation incidence

Personal communication from Dr. Joel Weinstock

The Hygiene Hypothesis Has Recently Been Questioned

Improved hygiene in some developing countries was not paralleled by increased autoimmune diseases

Celiac Disease
Autoimmune Epidemics



Necessary but <u>NOT</u> sufficient

The Epidemics of Celiac Disease:

Which Additional Factors are Driving this Epidemic?

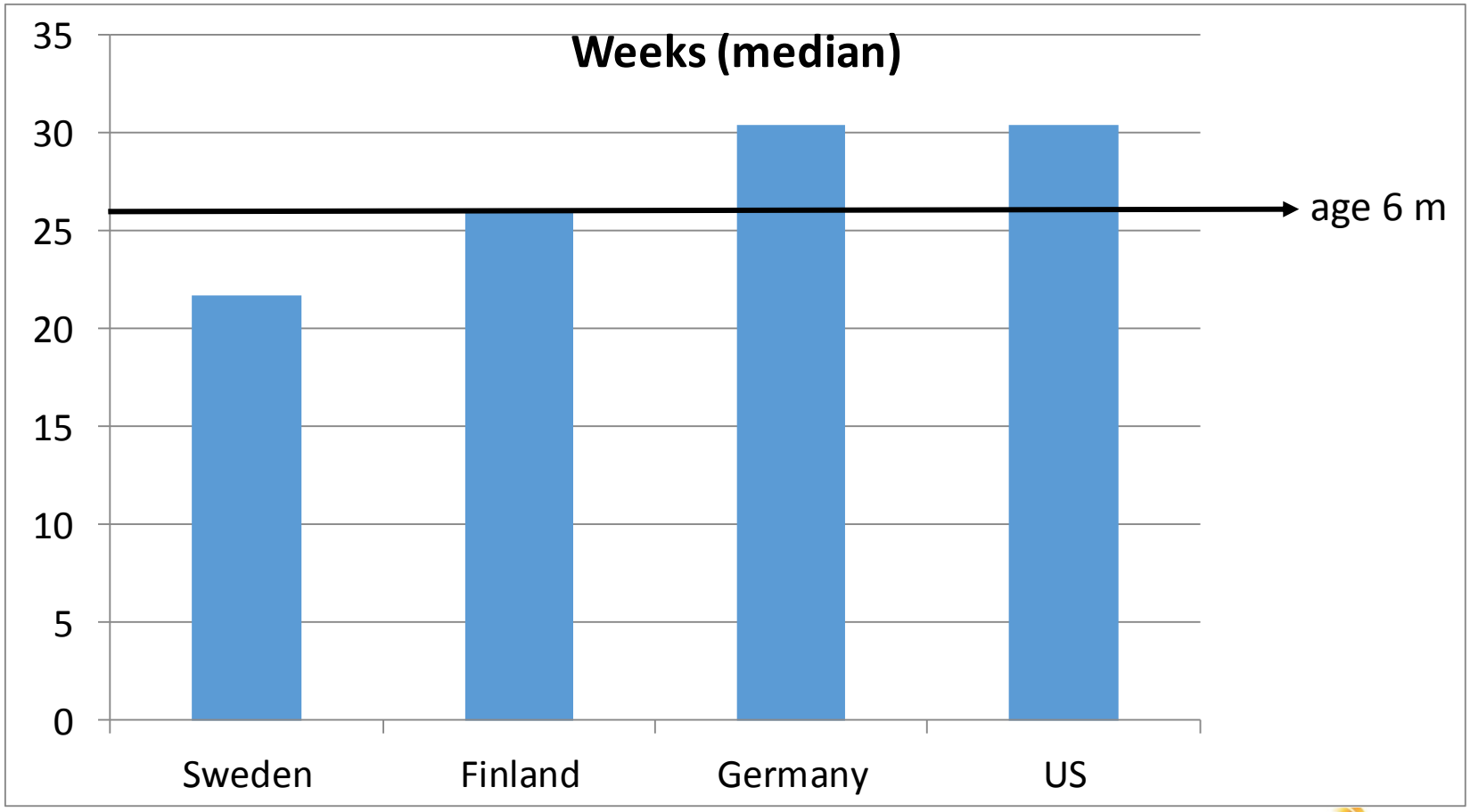
- Quality of gluten: Genetically engineered (GE) grains
- Quantity of gluten;
- Breast Feeding;
- Timing of gluten introduction
- Maturity of gut functions influencing Ag trafficking and handling:
  - GALT
  - PRRs
  - Mucous production
  - Barrier function
- Changes in microbiome composition.

Timing of Gluten Introduction and Risk of Celiac Disease: The CeliPrev Study

Carlo Catassi

Department of Pediatrics, Marche Polytechnic University, Ancona, Italy

Age at Gluten Introduction in Different Countries

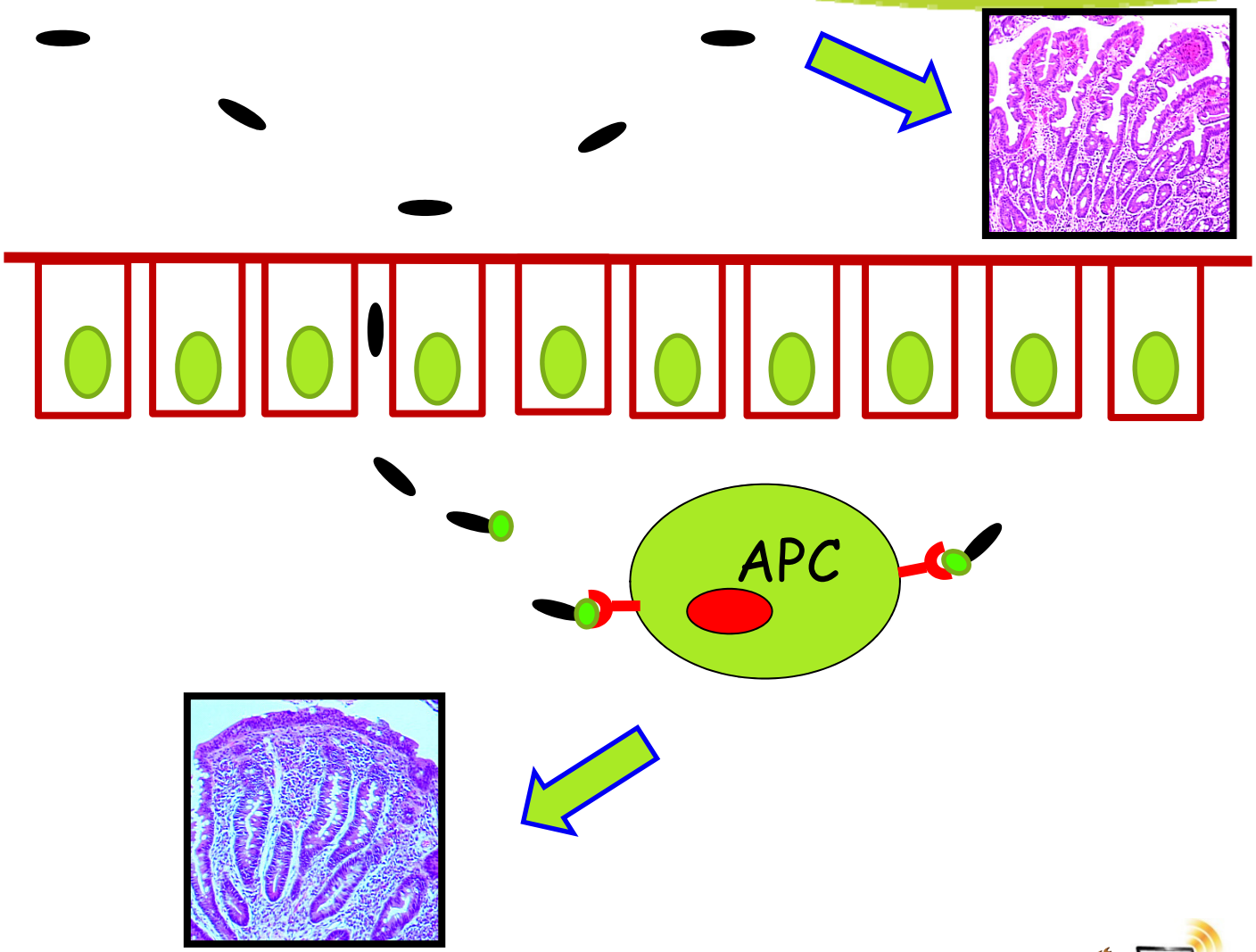


Aronsson CA et al, Pediatrics 2015

The CeliPrev Study Background

- Many parents spontaneously delay gluten introduction in at-family risk infants → does this attitude help to prevent celiac disease?

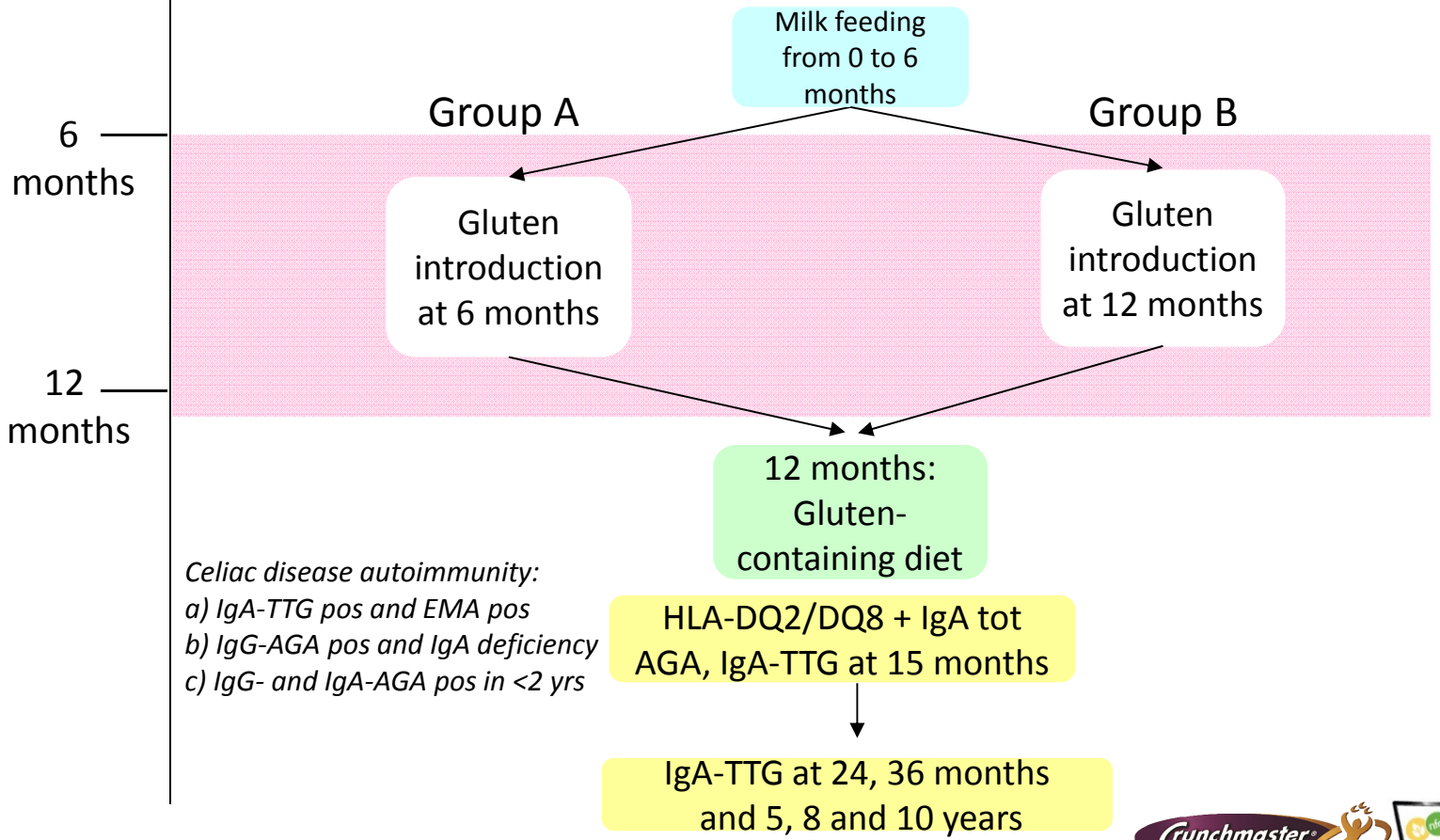
- Small intestinal permeability to macromolecules is increased during the first months of life → could early antigen avoidance prevent absorption of gluten peptides and celiac sensitization in genetically susceptible infants?



The CeliPrev Study Design

Infants at family risk of CD

Enrolment from 2003 to 2008 in 20 Italian centers

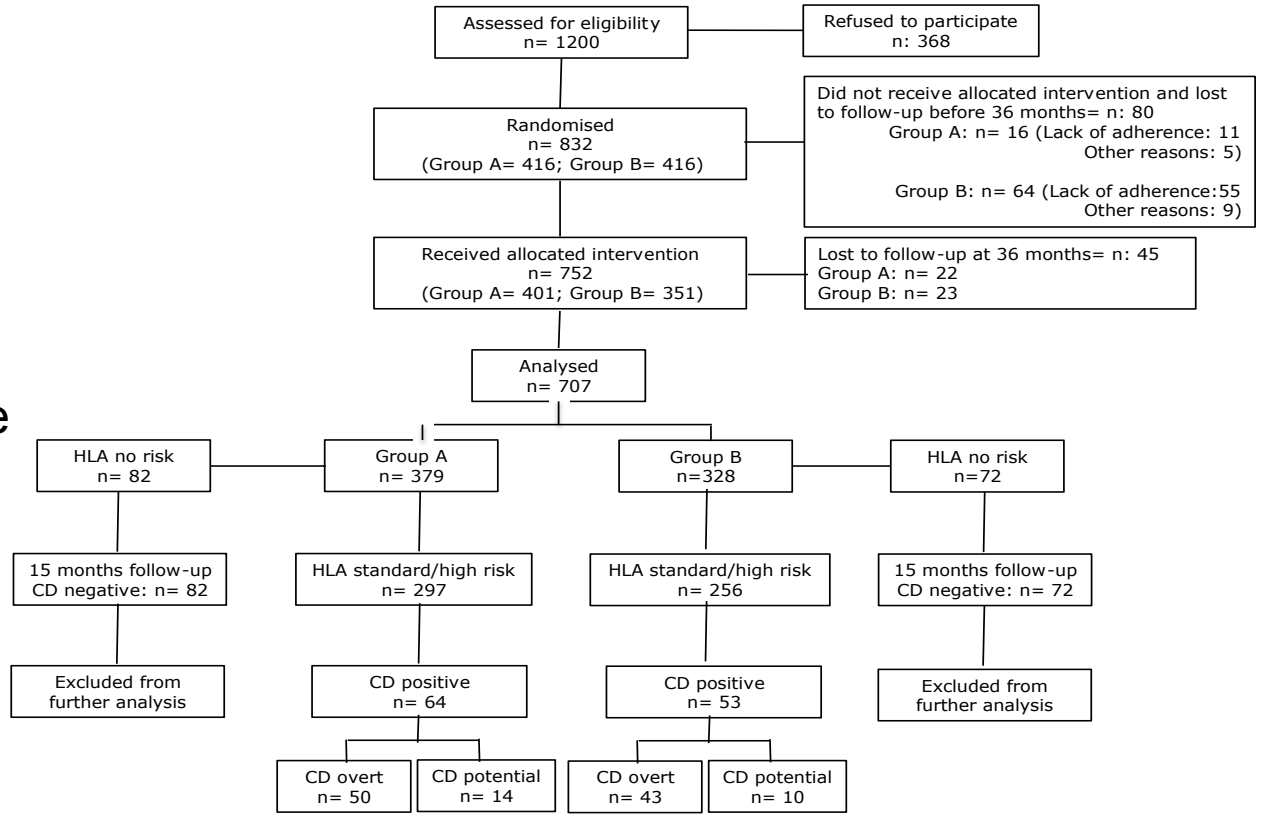


Associazione Italiana Celiachia

Flow Diagram of the Study

Study cohort n= 553

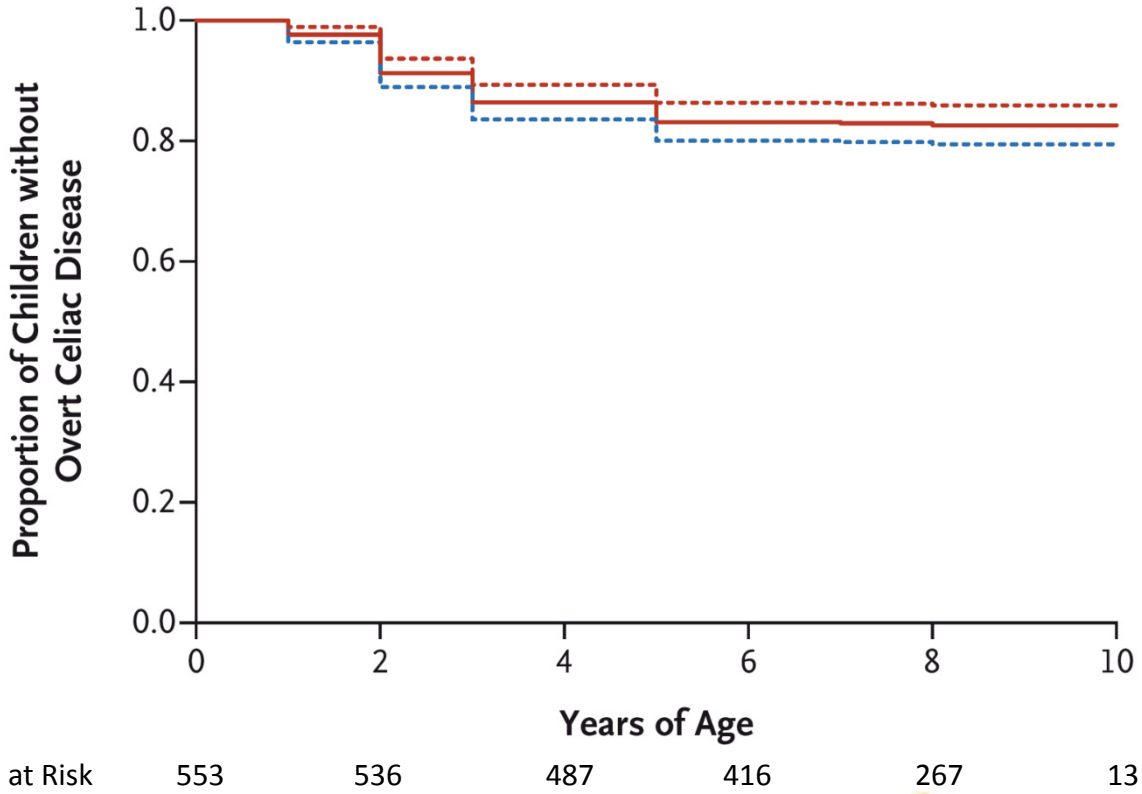
- Study Criteria: Newborns with at least one first-degree relative with celiac disease



Lionetti E et al; N Engl J Med 2014

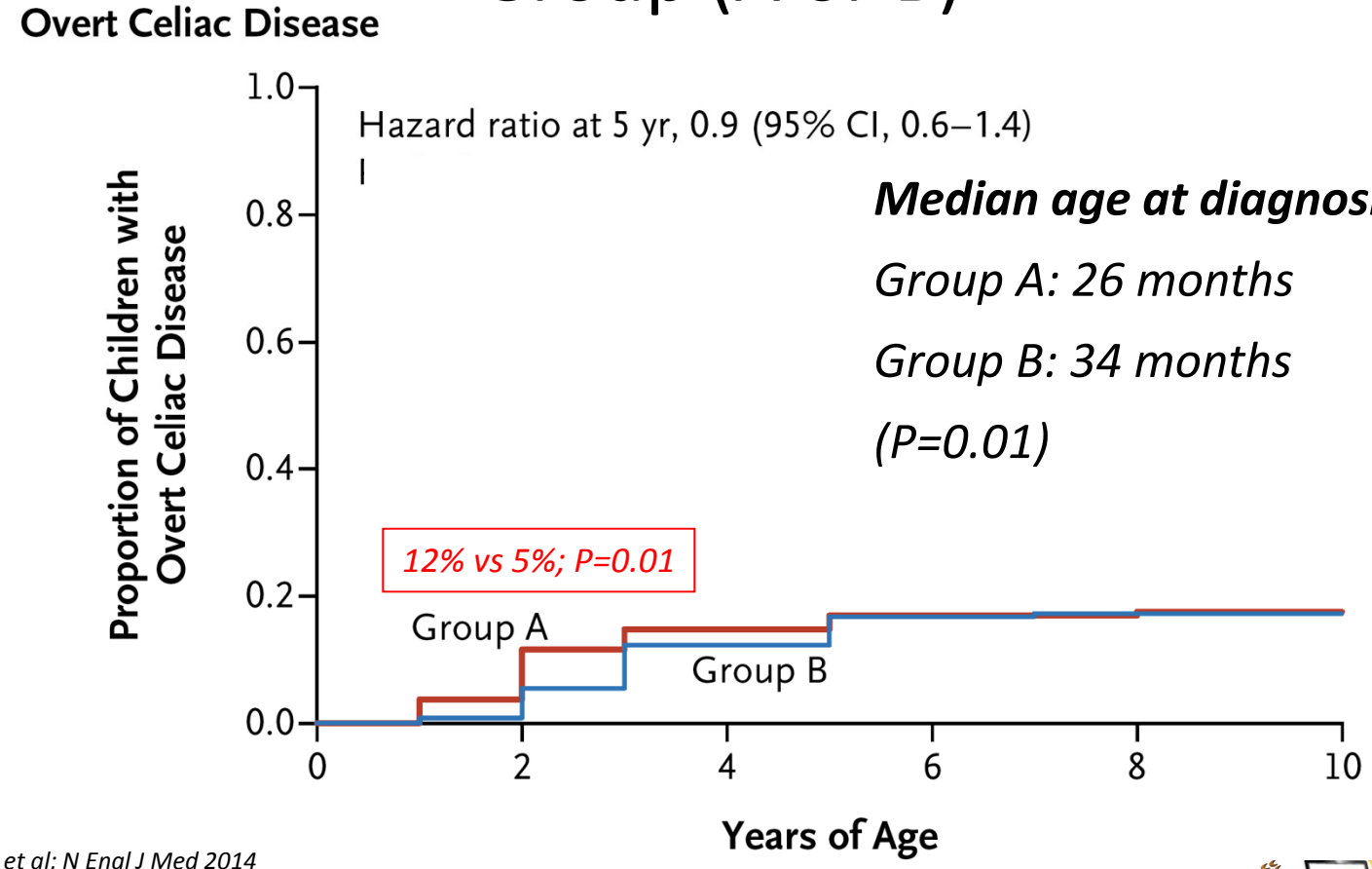
Estimates of Celiac Disease Prevalence in Children with HLA Predisposing-Genotype

Prevalence of overt celiac disease: 93/553 (16.8%)



Lionetti E et al; N Engl J Med 2014

Estimates of Celiac Disease According to Study Group (A or B)



Median age at diagnosis:

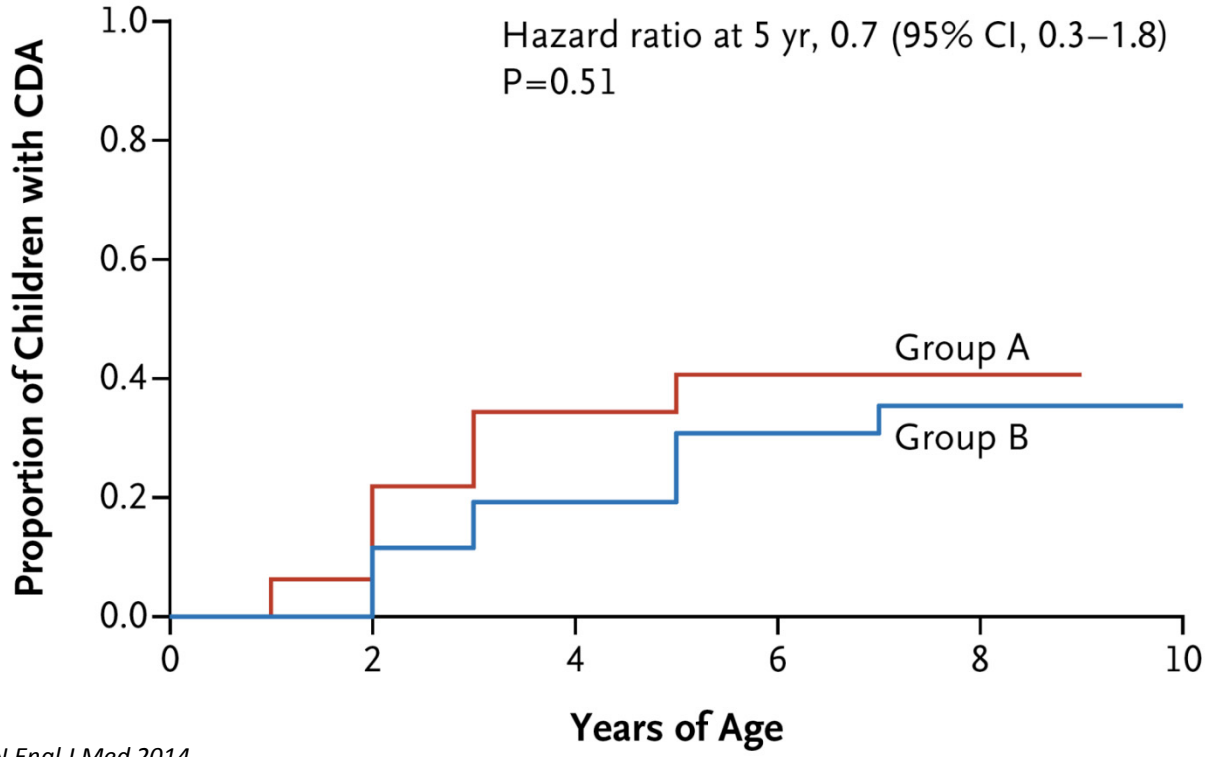
Group A: 26 months

Group B: 34 months

(P=0.01)

Lionetti E et al; N Engl J Med 2014

Estimates of Celiac Disease According to Study Group in Children with a Double Copy of HLA-DQ2 Genes

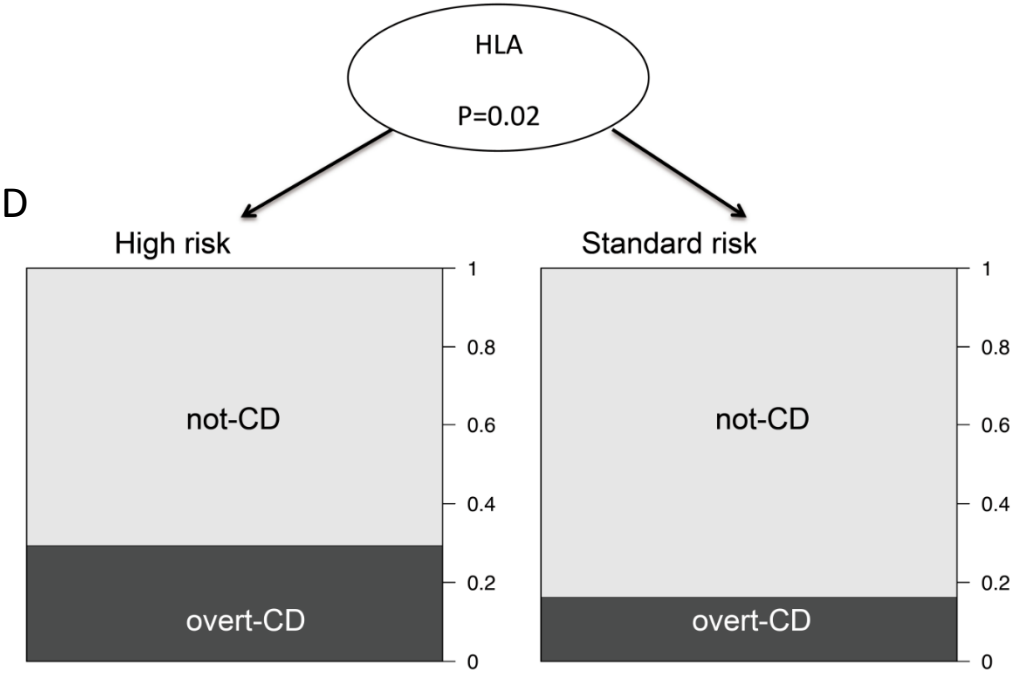


Lionetti E et al; N Engl J Med 2014

Decision Tree Analysis:
Variables Associated with Celiac Disease Development

Investigated Variables:

- Age
- Gender
- Number and type of relative with CD
- HLA genotype (single or double DQB1*02 copy)
- Amount of gluten
- Age at gluten introduction
- Trial arm
- Breast-feeding duration
- Breast-feeding during gluten introduction
- Intestinal infection



Lionetti E et al; N Engl J Med 2014

Timing of Gluten Introduction and Risk of Celiac Disease: From Scientific Evidence Back to Tradition

Infants with a family risk of celiac disease

1. Most children developing celiac disease do so within the first 5-6 years of life
2. Postponing the introduction of gluten did not reduce the overall risk of celiac disease, but simply delayed the disease development
3. Further studies are required to clarify whether postponing the introduction of gluten reduces the prevalence of celiac disease in children with a double copy of HLA-DQ2
4. HLA genotype was the only risk factor significantly associated to the development of celiac disease
5. Breast-feeding had no protective effect against celiac disease development (not shown in this presentation)

Lionetti E et al; N Engl J Med 2014

Gluten introduction at 6 months is ok but….

Some specific issues need to be addressed by further studies

The PreventCD study

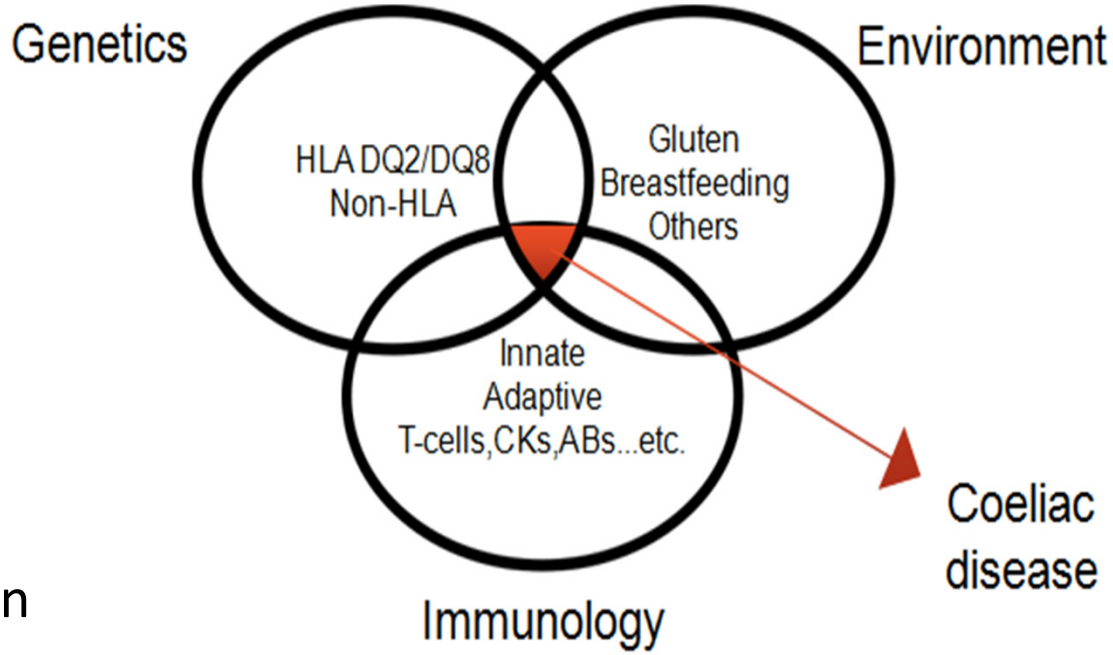
Randomized feeding intervention in infants at high risk for celiac disease

Dr. S.L. Vriezinga
PhD fellow pediatric gastroenterology
Leiden University Medical Center
The Netherlands
s.l.vriezinga@lumc.nl

PreventCeliacDisease.com

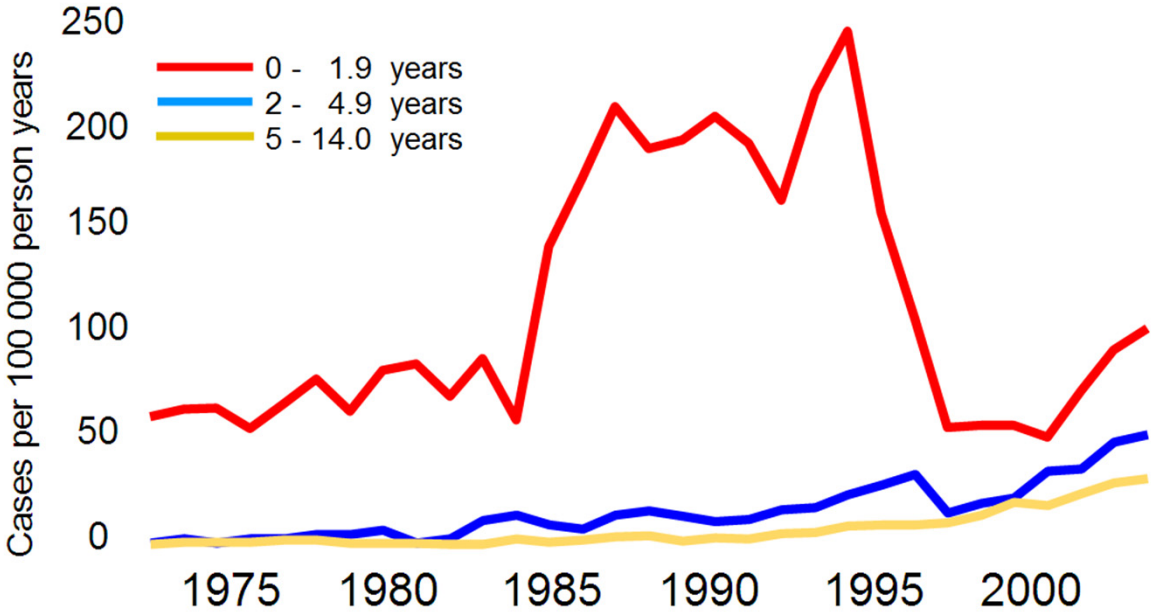
Prevent Celiac Disease

- **Quick Review:** 3 factors needed to develop celiac disease
  - Genetics
  - Immunology
  - Environmental trigger
- PreventCD focuses on environmental factors



Swedish Celiac Disease Epidemic

- From 1985-1987, pediatric cases of celiac disease drastically increased
- Guidelines on breastfeeding and gluten introduction had recently changed



Ivarsson A, Acta Paedatr 2000

Family Study PreventCD

Hypothesis:

Childhood celiac disease may be prevented

By introducing gluten:

- In small amounts
- 4-6 months of age
- Preferably breastfeeding

Design: Prospective, randomized, double-blind, placebo-controlled (PRDBPC)

Cohort: high-risk children

Endpoint:

50% ↓ celiac disease at age 3 years

www.preventcd.com

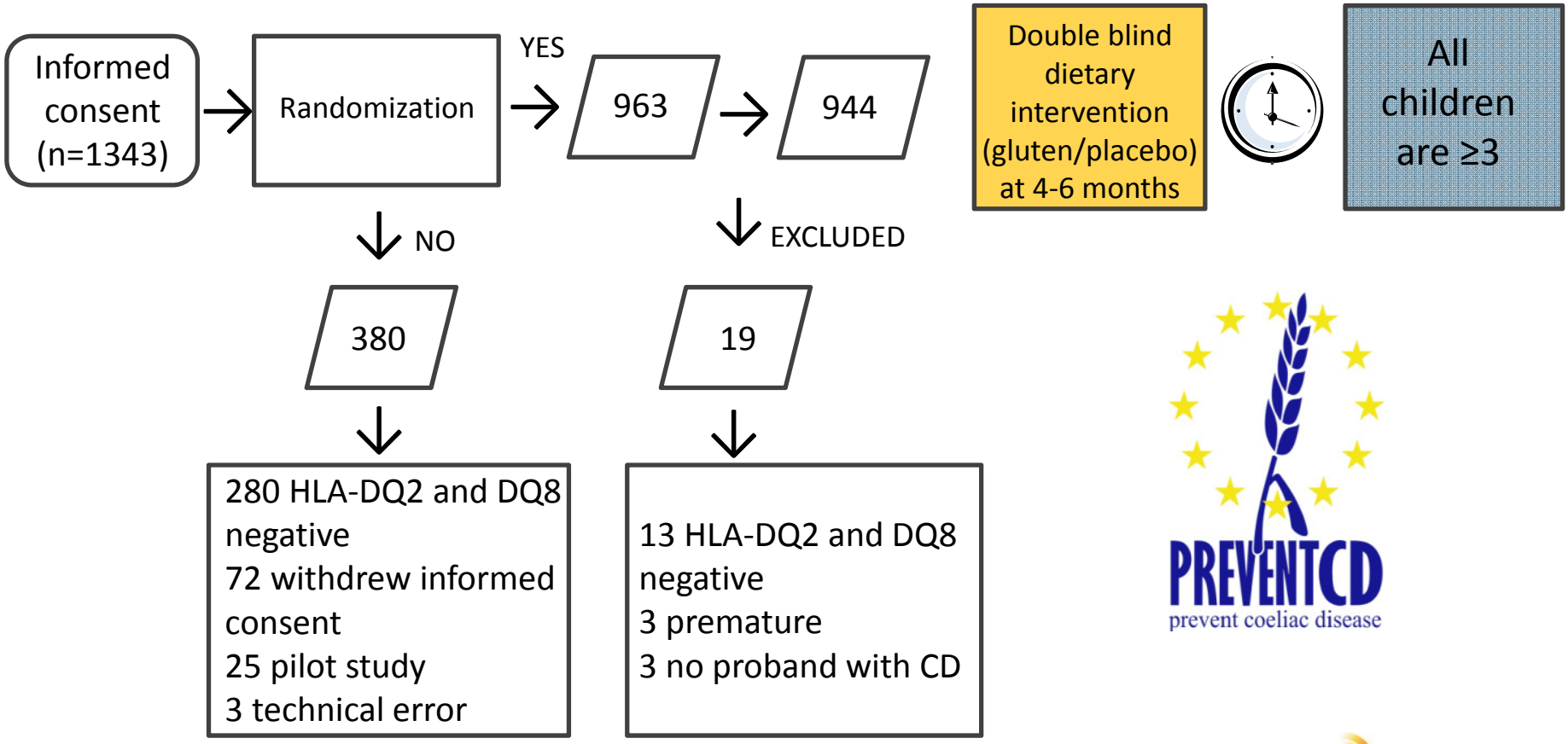
PreventCD

17 Partners: Hospitals, Labs and Industry

PREVENTCD
prevent coeliac disease

Crunchmaster Webinars

Large Recruitment Effort 2007-2010

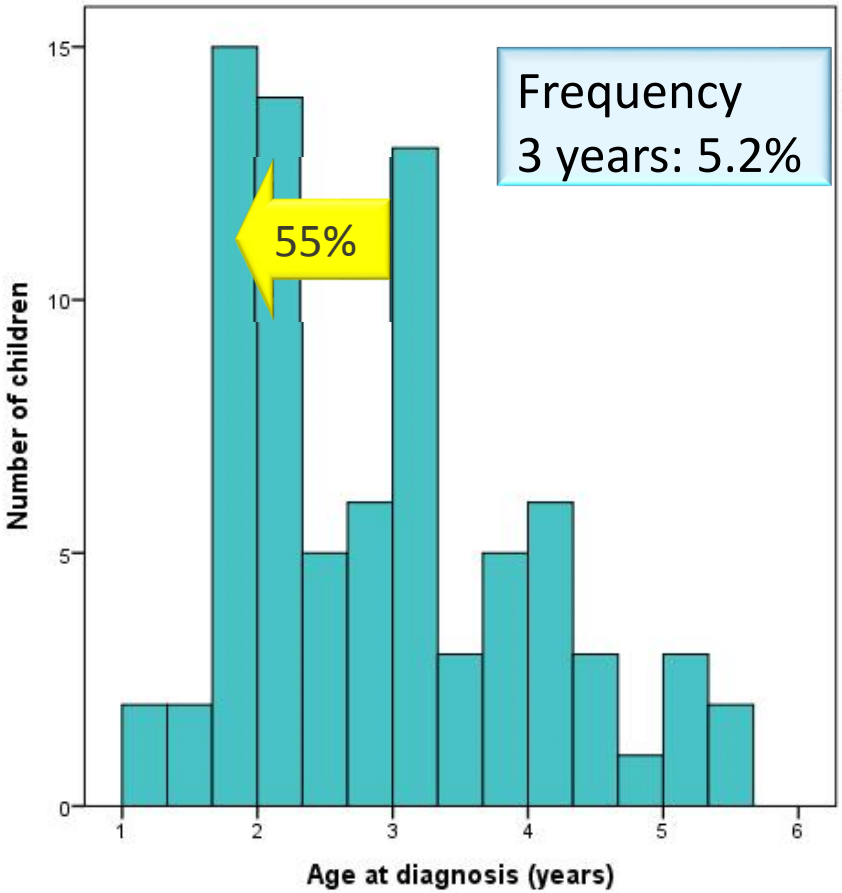


PREVENTCD
prevent coeliac disease

Methods

- Researchers regularly followed up with participants to:
  - Measure height, weight, and head circumference
  - Check general health
  - Monitor foods they were eating
  - Sample breast milk and blood
  - Check for serological markers

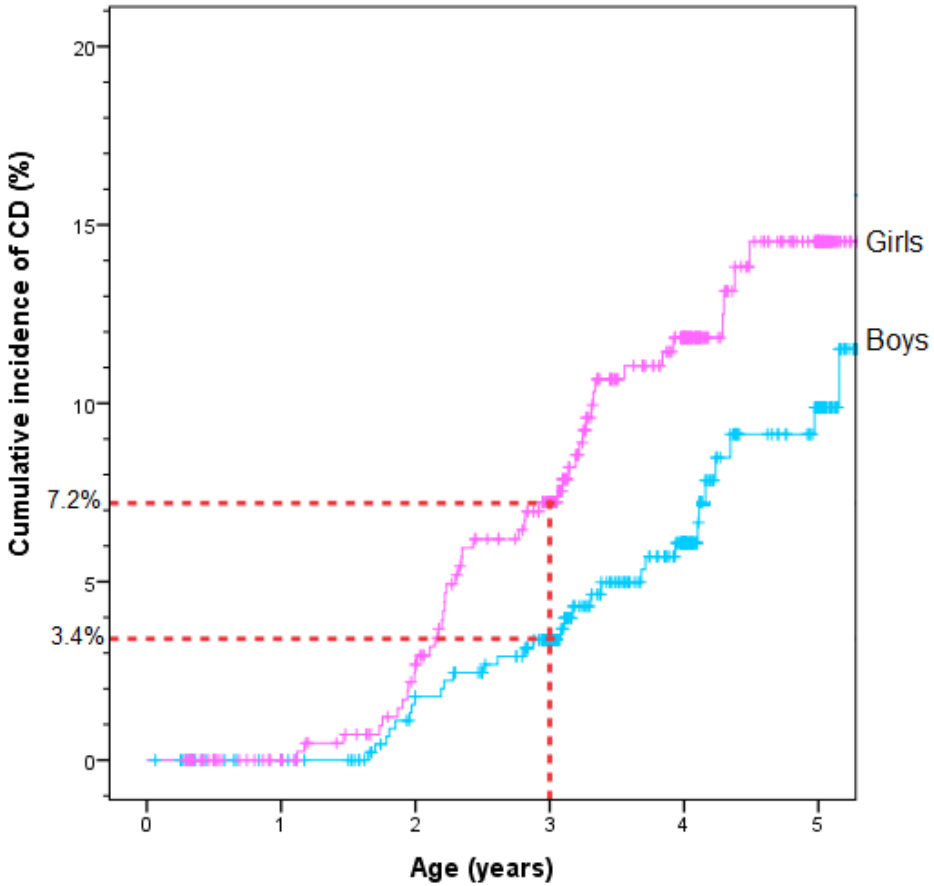
Age at Diagnosis of Celiac Disease



- Mean age at diagnosis = 2.8 years
- SD = 1.1 years
- Number of children diagnosed = 80/944
- Girls made up 59% of children who were diagnosed

Frequency of Celiac Disease According to Sex:

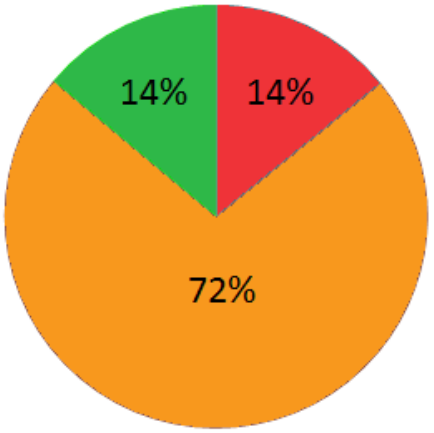
Girls Diagnosed More Frequently than Boys



P=0.04

Frequency of Celiac Disease According to HLA-haplotype

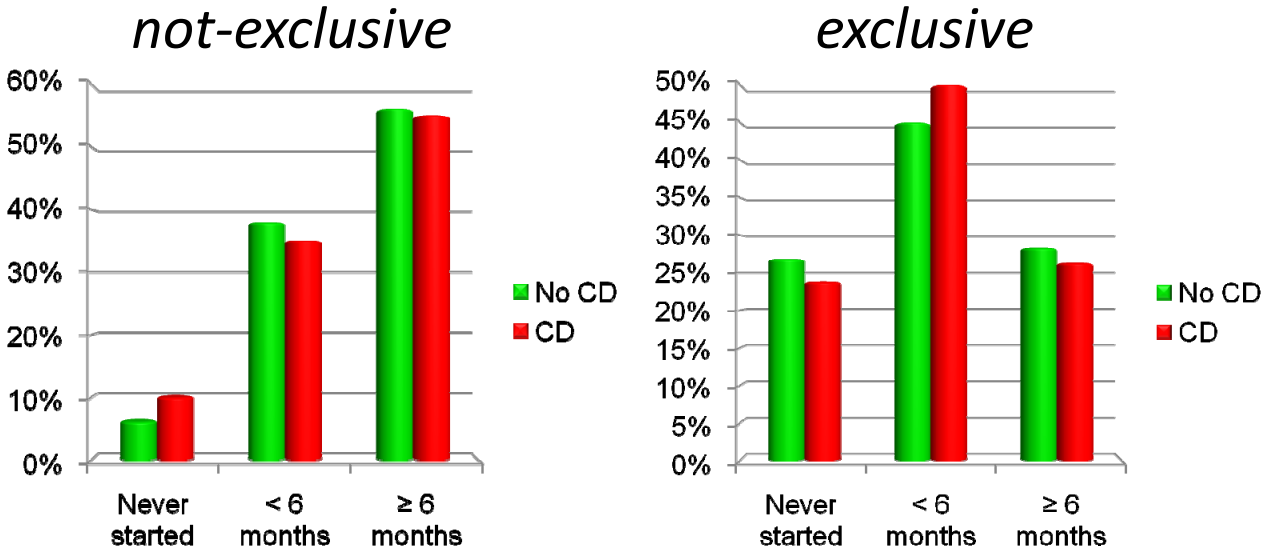
Haplotype	Cumulative incidence of CD at 3 years (%)
Homozygous DQ2	14.9
Heterozygous DQ2	3.9
DQ8	0.9



P<0.001

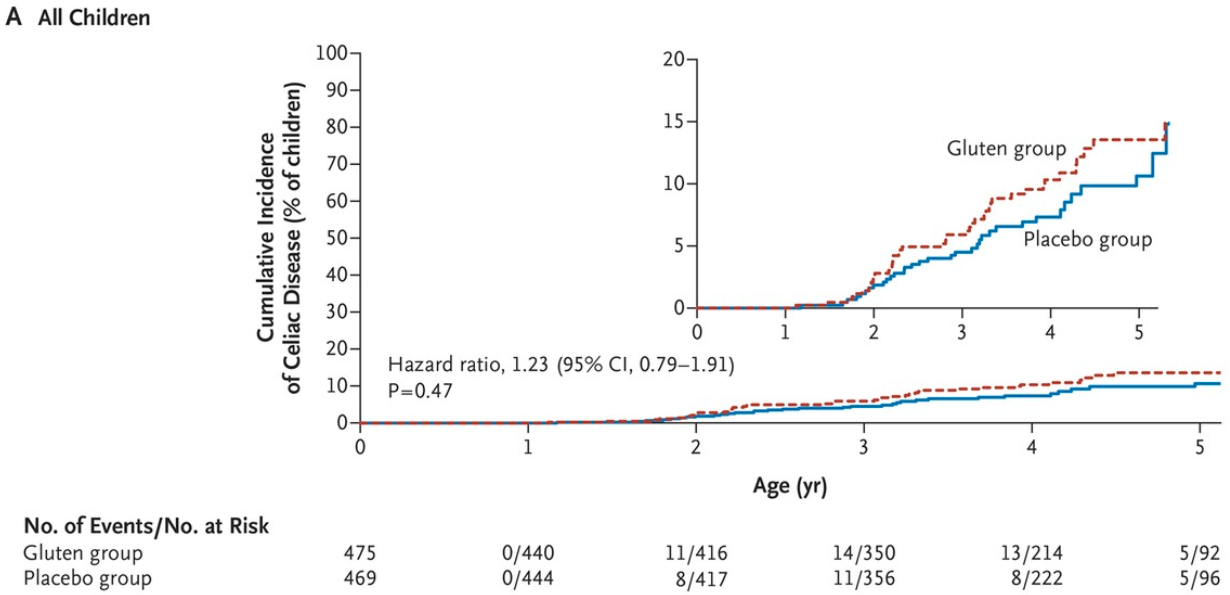
Not Related to the Development of Celiac Disease

Duration of breastfeeding



Frequency of Celiac Disease According to Gluten/Placebo

- Gluten group received 200mg vital wheat gluten mixed with 1.8g lactose
- Placebo group received 2g lactose



Vriezinga SL et al. N Engl J Med 2014

Conclusions

- Coeliac disease is **not prevented by introducing small amounts of gluten at age 4 months**
- Giving **breastfeeding does not reduce** the risk for coeliac disease
- Coeliac disease develops **already at a very young age**
- Significantly more often in **girls**
- Significantly more often in children homozygous for **HLA-DQ2**

Take Home Messages

- Window of tolerance concept (4-7 months best period to introduce baby food) not supported anymore
- Breastfeeding in general or introduction of gluten while breast feeding showed no protective effect on celiac disease onset in at-risk infants
- Early introduction (16 weeks) of traces of gluten to potentially induce tolerance did not protect against celiac disease in at-risk infants

Take Home Messages, Continued

•Delaying the introduction of gluten in at-risk infants does not prevent celiac disease but merely postpones its onset by approximately 8 months (significant difference at 2 years follow-up that disappeared by 5 years follow-up)

•Gastrointestinal infections during the first year of life seems influential in increasing the risk of celiac disease onset

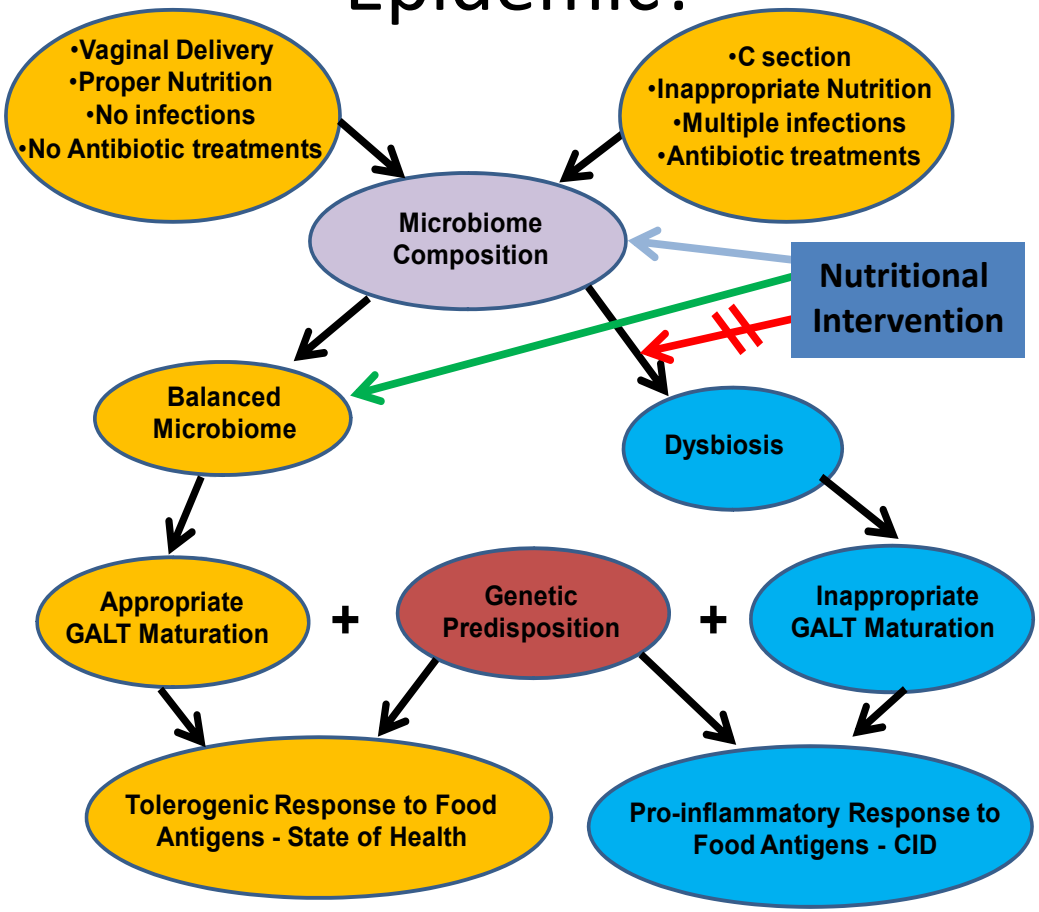
•High-risk HLA profiles seems to be the most influential factor predictor of increased risk of celiac disease onset

•The high prevalence of celiac disease among the study cohort suggests that the celiac disease epidemic continues

The Epidemic Of Celiac Disease:
Which Additional Factors are Driving this Epidemic?

- Quality of gluten;
- Quantity of gluten;
- Breast Feeding;
- Timing of gluten introduction
- Maturity of gut functions influencing Ag trafficking and handling:
    - GALT
    - PRRs
    - Mucous production
    - Barrier function
- Changes in microbiome composition.

Which Factors are Driving This Autoimmunity Epidemic?



Celiac **D**isease **G**enomic **E**nvironmental **M**icrobiome and **M**etabolomic Study

Hypothesis

Combination of introduction of gluten into the diet and particular microbiota composition of infants genetically at risk for CD activates specific metabolic pathways that can contribute to the loss of tolerance to gluten and to the onset of autoimmunity, as reflected by specific metabolomic phenotypes.

www.CDGEMM.org

Crunchmaster® Webinars

As we finish…

Questions from the audience?

Thanks to our sponsor!

www.crunchmaster.com

www.harveststonesnacks.com

www.facebook.com/crunchmaster

Watch and Win a Crunchmaster Gift Basket!

- Crunchmaster® Multi-Seed Crackers in 3 Flavors:
  - Original
  - Roasted Garlic
  - Rosemary & Olive Oil
- Crunchmaster® Multi-Grain Crackers in 3 Flavors:
  - Sea Salt
  - Roasted Vegetable
  - White Cheddar

- HarvestStone® Crispy Mix in 3 Flavors:
  - Original
  - Cheese
  - Bold

PLUS these other Crunchmaster goodies:

Crunchmaster® Webinars

NFCA Resources

- celiaccentral.org/riskfactors/
- celiaccentral.org/research-news/
- celiaccentral.org/researchoptin/

Save the Date!
CeliacCentral.org/webinars

Topic: "The Right Time, The Right Place, The Right Conversation: Talking to Your Family Members About Celiac Disease Testing"

Date: Thursday, May 14th

Time: 8 p.m. Eastern/5 p.m. Pacific

Speakers: Kristin Voorhees, M.A., and Christina Gentile, Psy.D.

Thank You!

- Webinar questions, comments, feedback: webinars@CeliacCentral.org

- Connect with NFCA: