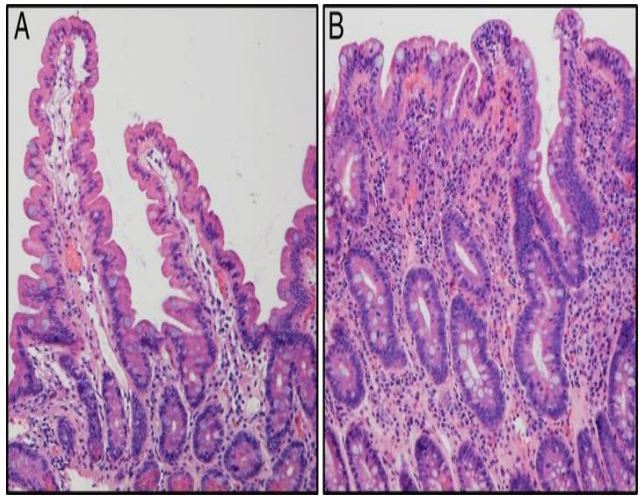
Non-Celiac Gluten Sensitivity – A True Disease or Misdiagnosis?



Nicholas J. Talley, MD, PhD

DISCLOSURES

Nicholas Talley, M.D.

- **Consultant** - Aviro Health ,Allakos, Anatara Life Sciences, Cadila Pharmaceuticals, Censa, Progenity Inc., Planet Innovation, Sanofi-aventis, Takeda, twoXAR, Viscera Labs
- **Grant/Research Support** - HVN National Science Challenge NZ (no financial support) March 2019
- **Honoraria**- Aviro Health ,Allakos, Anatara Life Sciences, Cadila Pharmaceuticals, Censa, Progenity Inc, Planet Innovation, Sanofi-aventis, Takeda, twoXAR, Viscera Labs
- **Full-time/Part-time Employee** - University of Newcastle, Medical Journal of Australia , Up to Date, Precision and Future Medicine, Sungkyunkwan University School of Medicine, South Korea
- **Other:** Australian Medical Council (AMC) Council Member, MBS NHMRC Principal Committee, Research Committee, Asia Pacific Association of Medical Journal Editors, Patents MBS Review Taskforce, AAHMA Member

Learning Objectives

Upon conclusion of this program, participants should be able to:

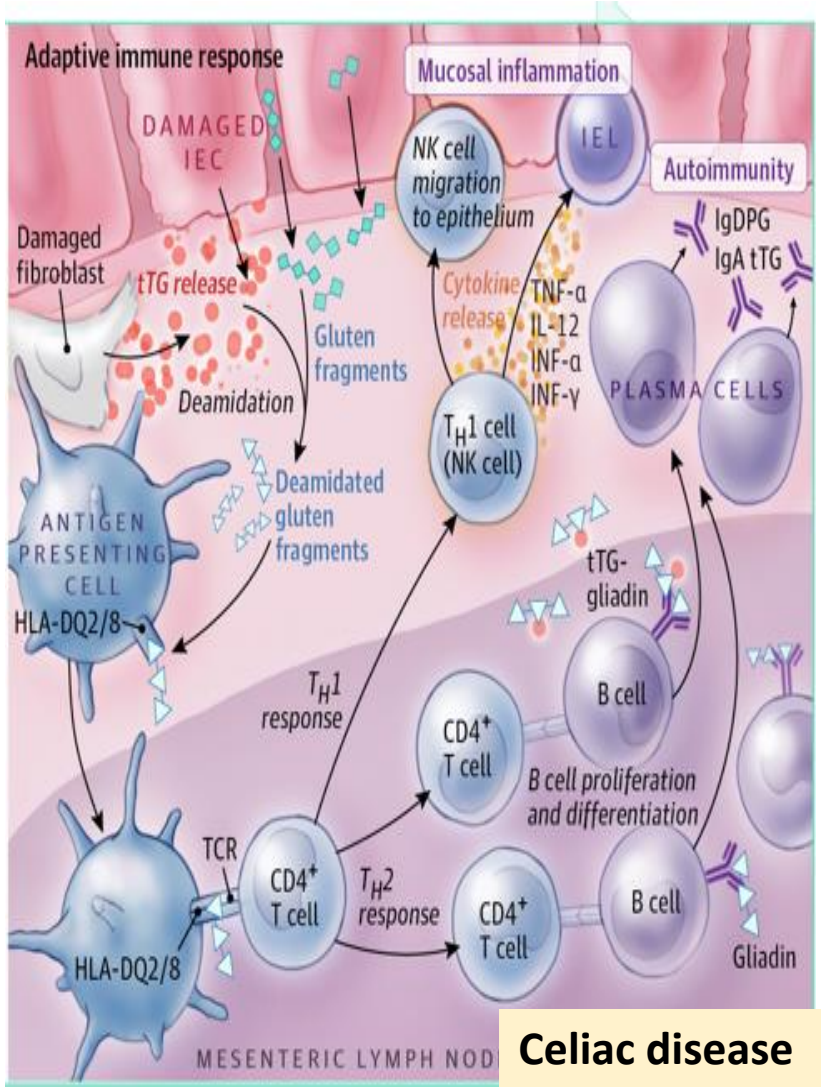
- Distinguish non-celiac gluten sensitivity (NCGS) from wheat allergy, celiac disease and “celiac lite” cases
- Identify the relationship between functional GI disorders (IBS and functional dyspepsia) and NCGS
- Recognize new potential biomarkers of NCGS including duodenal pathology (eosinophils) and immune activation
- Estimate the benefits versus risks of a gluten free diet in NCGS

Case

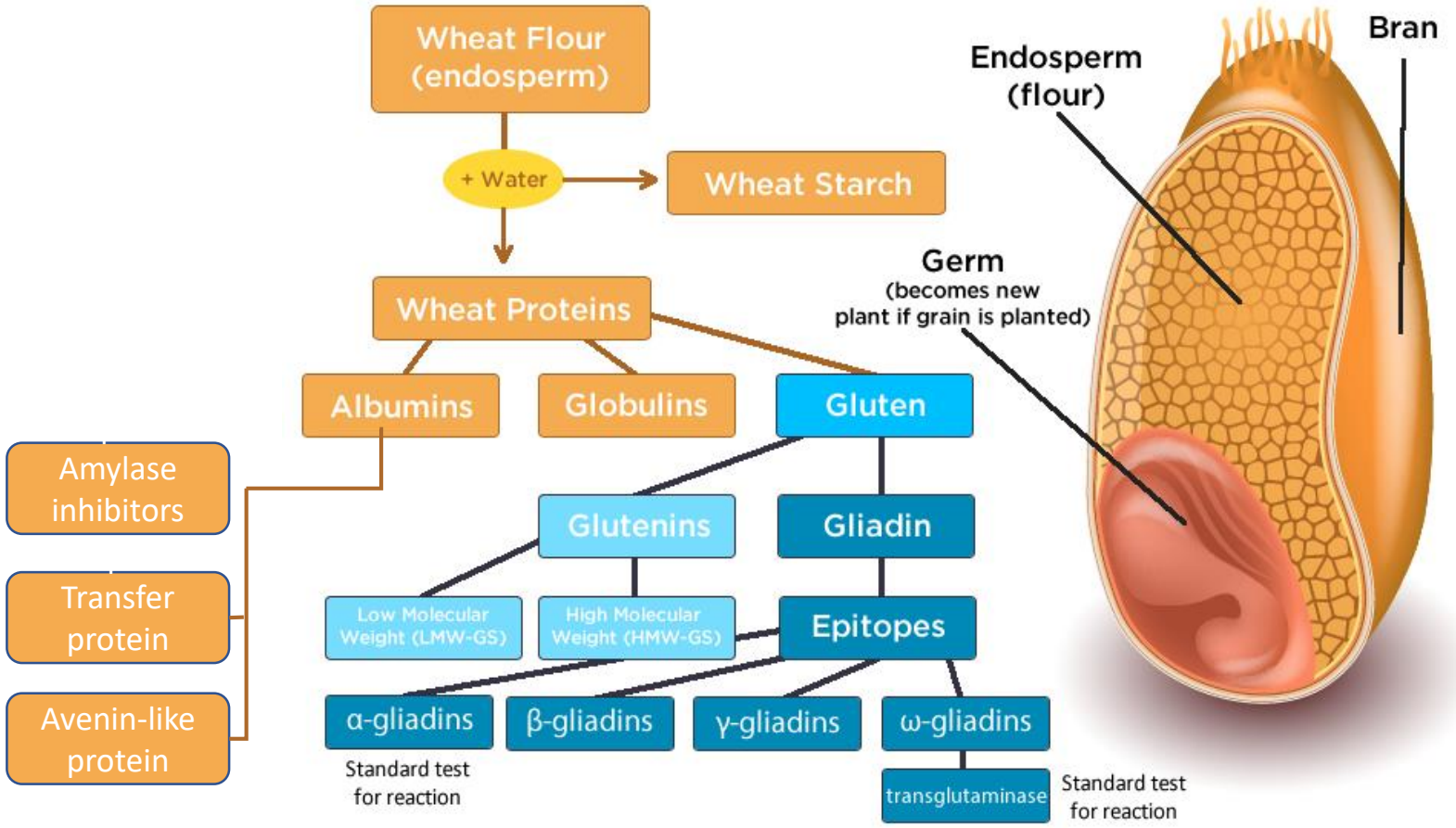
- 25 year old woman with 10 year history of daily bloating, abdominal pain after eating, loose stools and pain relief on defecation, early satiety, heartburn, lethargy, joint pain, light headedness, headaches and anxiety
- Been on a gluten free diet with partial relief of symptoms only
- No red flags, past history of well controlled asthma
- Mother has celiac disease and is on a strict gluten free diet
- Exam normal, BMI 20
- tTG negative (IgA normal), previous EGD normal & a normal duodenal biopsy (testing on a gluten free diet)
- HLA-DQ2 positive
- She is worried celiac disease might have been missed, and if it's not celiac, worried what is wrong with her?
- She wants to know should she stay on a strict gluten free diet? Any risks if she does?
- What diagnostic label would you apply?:
    A. Celiac disease
    B. Subclinical celiac disease
    C. Non-celiac gluten sensitivity
    D. Irritable bowel syndrome
    E. Functional (non-ulcer) dyspepsia
    F. Wheat allergy
    G. Anxiety

Wheat and celiac disease

Leonard et al.
JAMA. 2017;318:647-656



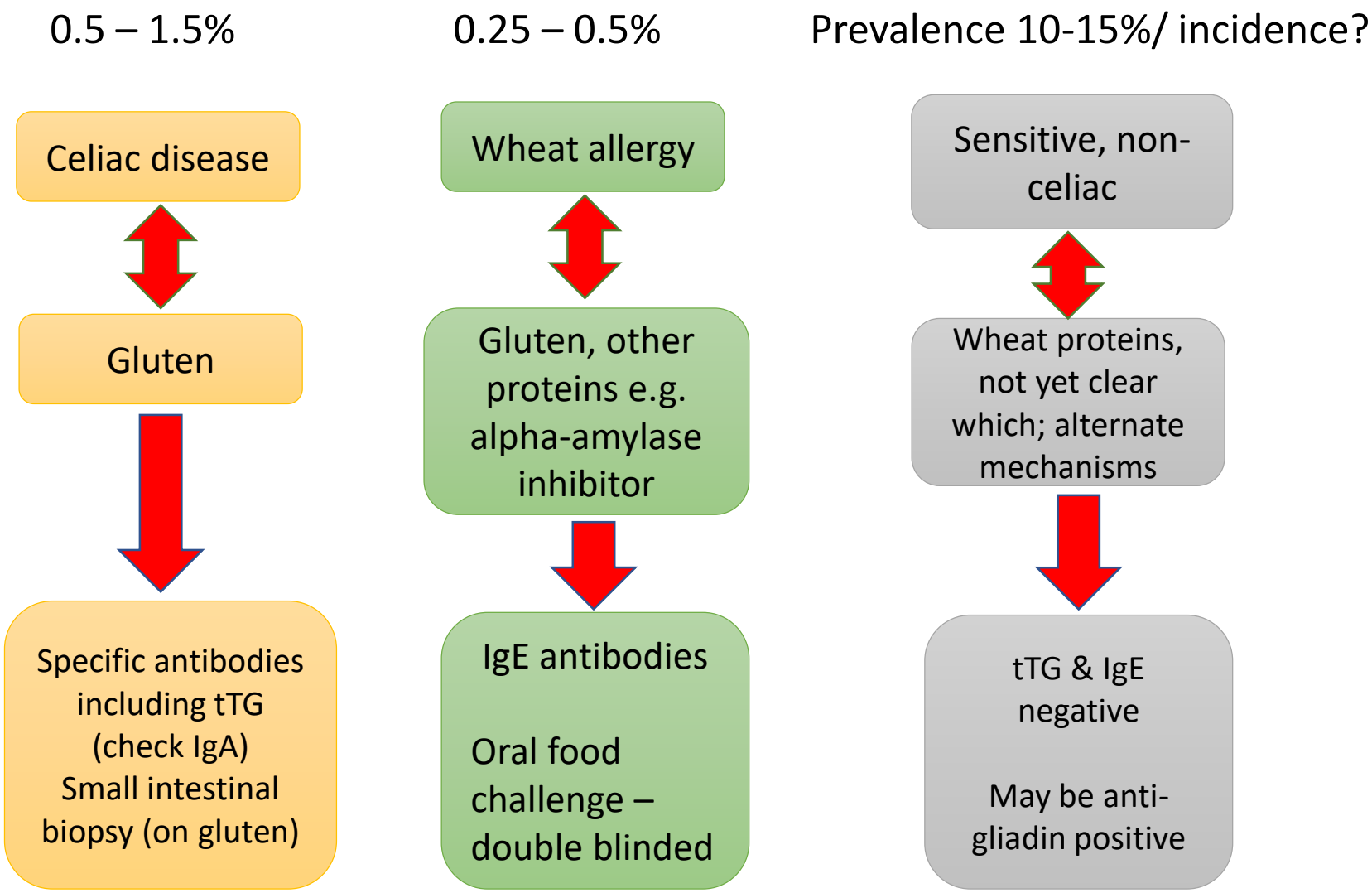
Celiac disease



Celiac disease:

- *Partially digested epitopes of gluten*
- *Aberrant immune reaction in genetically susceptible individuals (HLA DQ2/8)*
- *Incorporates an **adaptive T-cell-mediated response** (to gluten)*

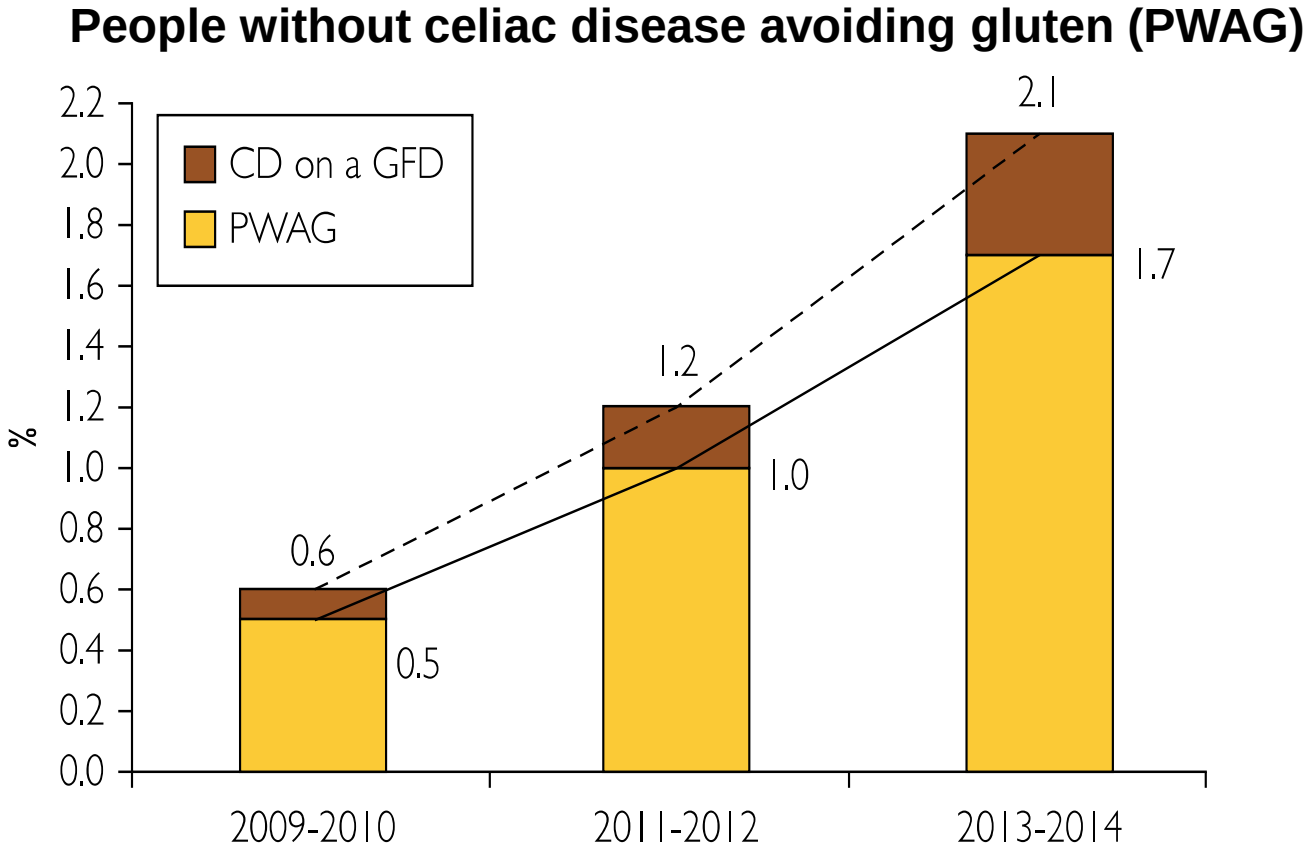
Wheat and Gluten: Allergy and Intolerance



Adapted from Catassi et al, Nutrient, 2015 & 2017

Gluten free dieters increasing

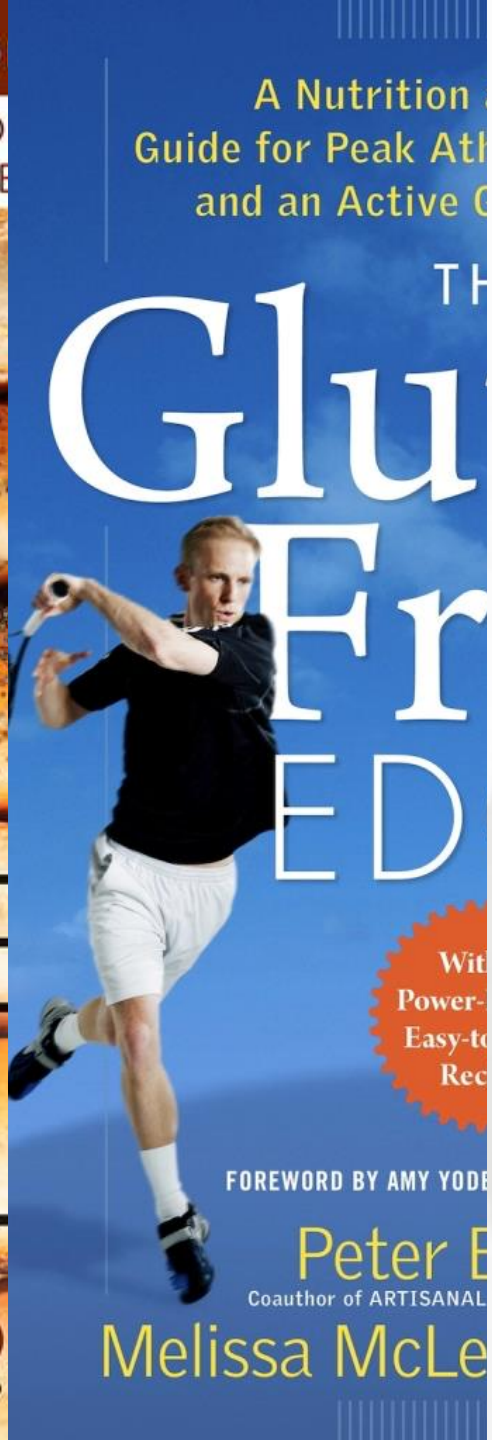
- Gluten avoidance is increasing
- Not explained by celiac disease
- **Why is it so?**



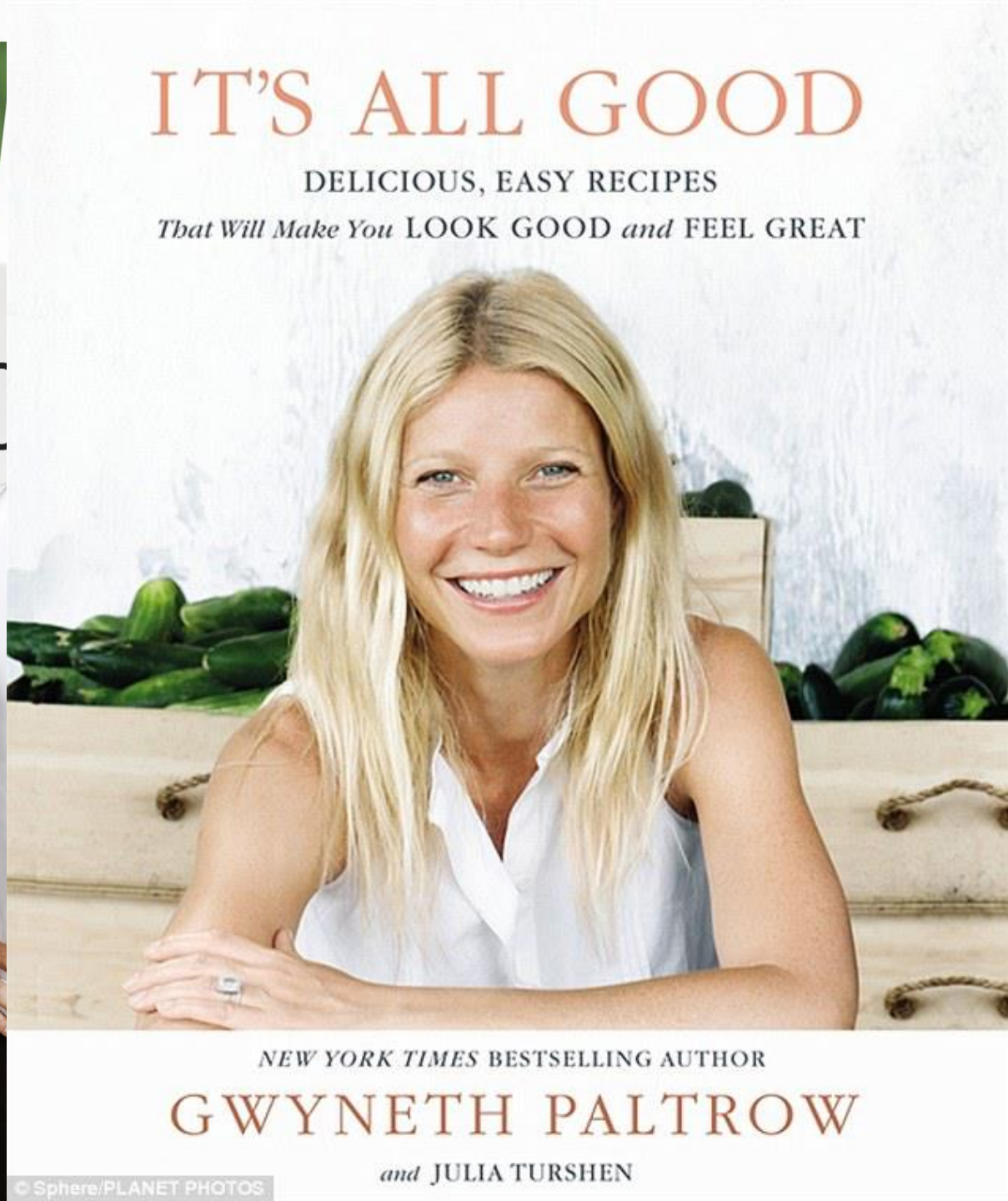
	NHANES 2009-2010 (n=7798)	NHANES 2011-2012 (n=6903)	NHANES 2013-2014 (n=7577)	*P* Value
Total GFD*	n=55, 0.6 (0.3-0.9)	n=75, 1.2 (0.7-1.7)	n=113, 2.1 (1.3-3.0)	.004
PWAG*	n=49, 0.5 (0.5-0.9)	n=69, 1.0 (0.6-1.4)	n=95, 1.7 (1.1-2.4)	.005

Choung RS et al. Mayo Clin Proc. 2016 doi: 10.1016/j.mayocp.2016.10.012


MORE THAN 1 MILLIO
LOSE THE WHEAT, LO
AND FIND YOUR PATH E
#1
NEW YORK
TIMES
BESTSELLER
WHE
BEL
WILLIAM D
WITH A NEW FOREWORD

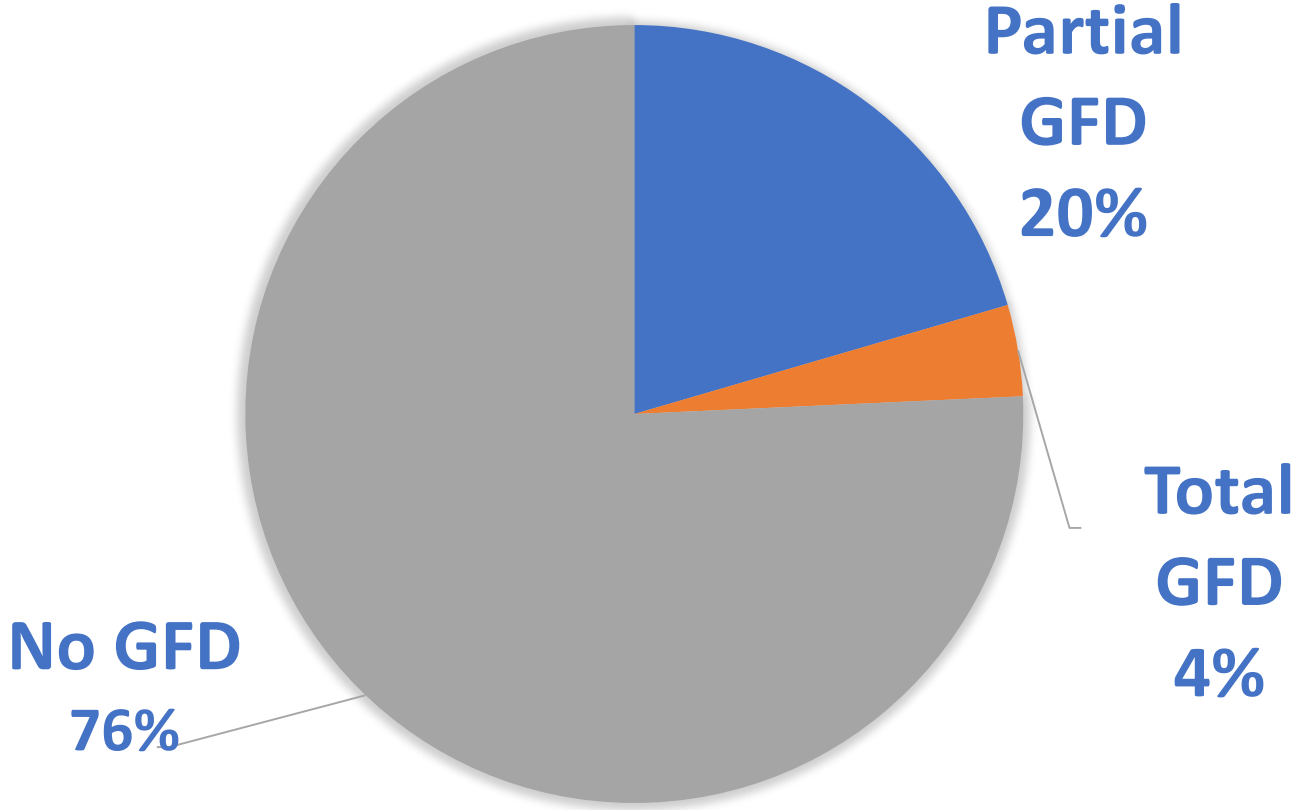

A Nutrition
Guide for Peak Ath
and an Active
TH
Glu
Fr
ED
Wit
Power-
Easy-to
Rec
FOREWORD BY AMY YODE
Peter E
Coauthor of ARTISANAL
Melissa McLe


SERV
NOVAK
DJOKOVIC


IT'S ALL GOOD
DELICIOUS, EASY RECIPES
That Will Make You LOOK GOOD and FEEL GREAT
NEW YORK TIMES BESTSELLING AUTHOR
GWYNETH PALTROW
and JULIA TURSHEN
© Sphere/PLANET PHOTOS

Gluten free diet popular: 1 in 4 Australians

- Digestive health and wellbeing study, validated survey in Australia
  - Longitudinal cohort study
    - ~8500 participants (electoral roll)
    - 2015: Questionnaire data on ~3500
    - 2018: Repeat symptomatic and dietary assessment~1200
    - Serum, fecal and biopsy samples from smaller subset
  - Mean age 59 years, 48% male
  - Celiac disease 1%



Potter, Talley et al. MJA 2020

Gluten vilified

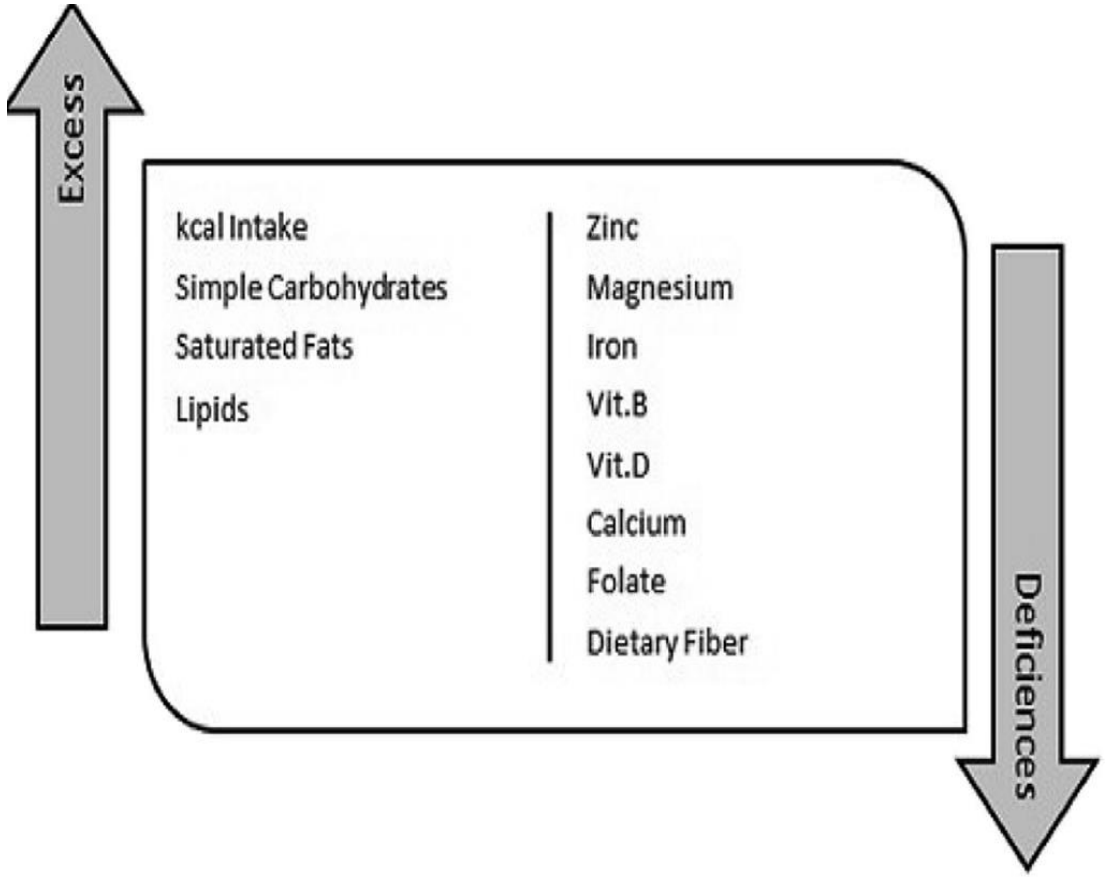
- Perception that gluten linked with
  - Weight gain
  - Poor general health
  - Decreased athletic performance
  - **Adverse physiological symptoms**

Effect of the gluten-free diet on cardiovascular risk factors in patients with coeliac disease: A systematic review

Michael D E Potter,*,† Stephen C Brienesse,*,† Marjorie M Walker,*,† Andrew Boyle*,† and Nicholas J Talley*,†

Journal of Gastroenterology and Hepatology **33** (2018) 781–791

- Studies looking at BP, BMI, blood glucose, lipids before and after a GFD
- 27 articles included of 5372 articles from 4 databases
- All celiac disease patients (no NCGS)
- 7 studies reported a significant INCREASE in BMI within the healthy weight range
- 2 studies reported increase in fasting BSL
- 3 studies reported increase in total cholesterol (largely due to an increase in HDL)
- 1 study found metabolic syndrome in 1/3 of subject after starting GFD



Vici et al. (2016) Clinical Nutrition

Heavy metals

- 7471 participants in NHANES (USA); 1.2% CD
- Higher urinary arsenic concentrations

- ?Rice (arsenic based pesticides)

	Gluten-Free Diet[a] N=73	Non-Gluten-Free Diet N=7,398	
Metal	**Geometric Mean (SE)[b]**	**Geometric Mean (SE)[b]**	**Geometric Mean Ratio (95% CI)[b]**
Urinary Concentrations			
Total arsenic (μg/L)	12.1 (1.5)	7.8 (0.23)	1.5 (1.2–2.0)
Estimated total arsenic 1 (μg/L)[c]	6.1 (1.0)	3.2 (0.14)	1.9 (1.3–2.6)

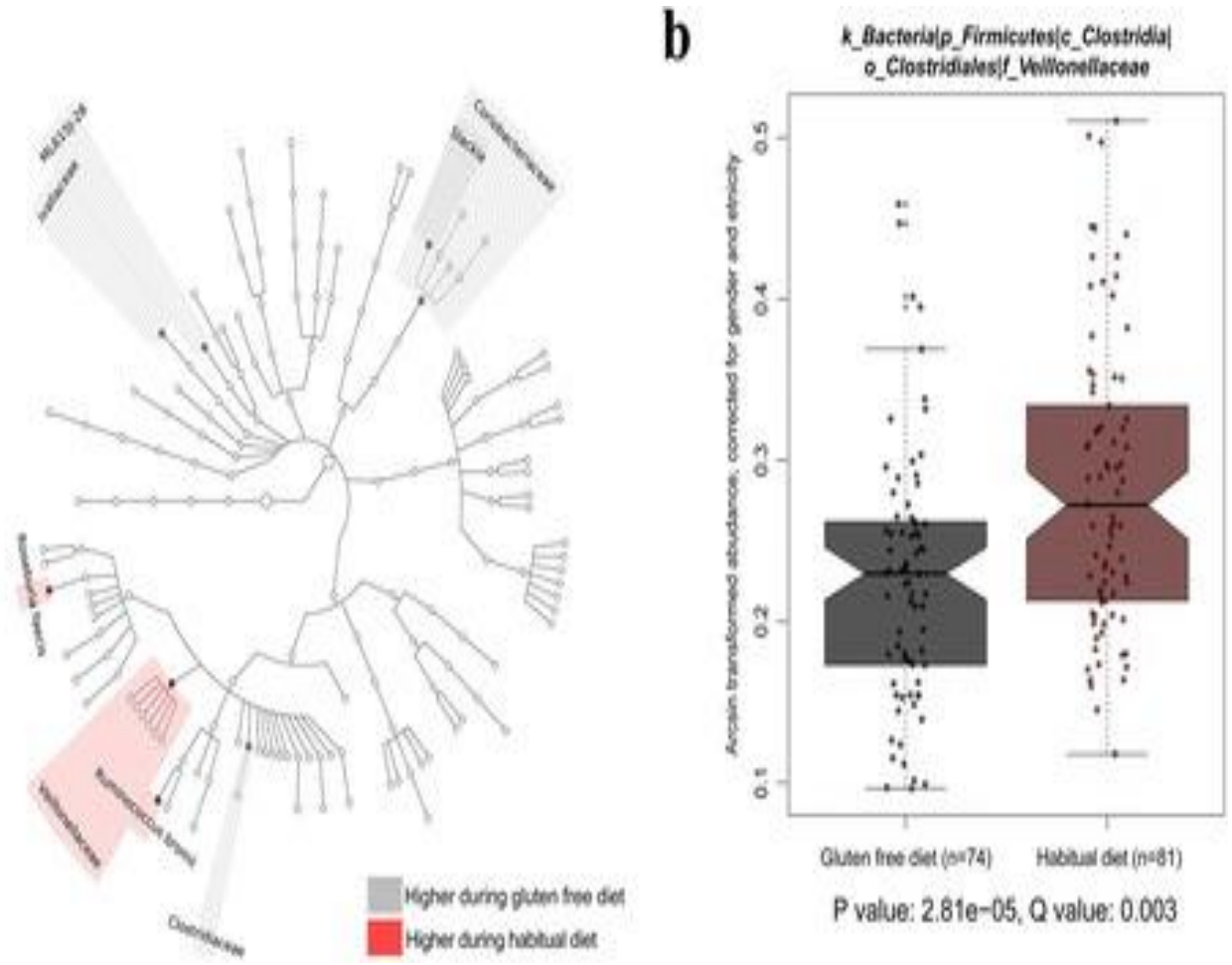
Bulka et al. Epidemiology. 2017;28(3) e24-25

Gluten free diet (GFD) and the microbiome

21 healthy volunteers a GFD for 4 weeks

Habitual diet and GFD time points, corrected for age and ethnicity on stool in MaAsLin:

- *Veillonellaceae* abundance dropped significantly on a GFD
- *Ruminococcus bromii* and *Roseburia faecis* abundance also dropped
- Families *Victivallaceae, Clostridiaceae*, and *Coriobacteriaceae* increased in abundance on a GFD

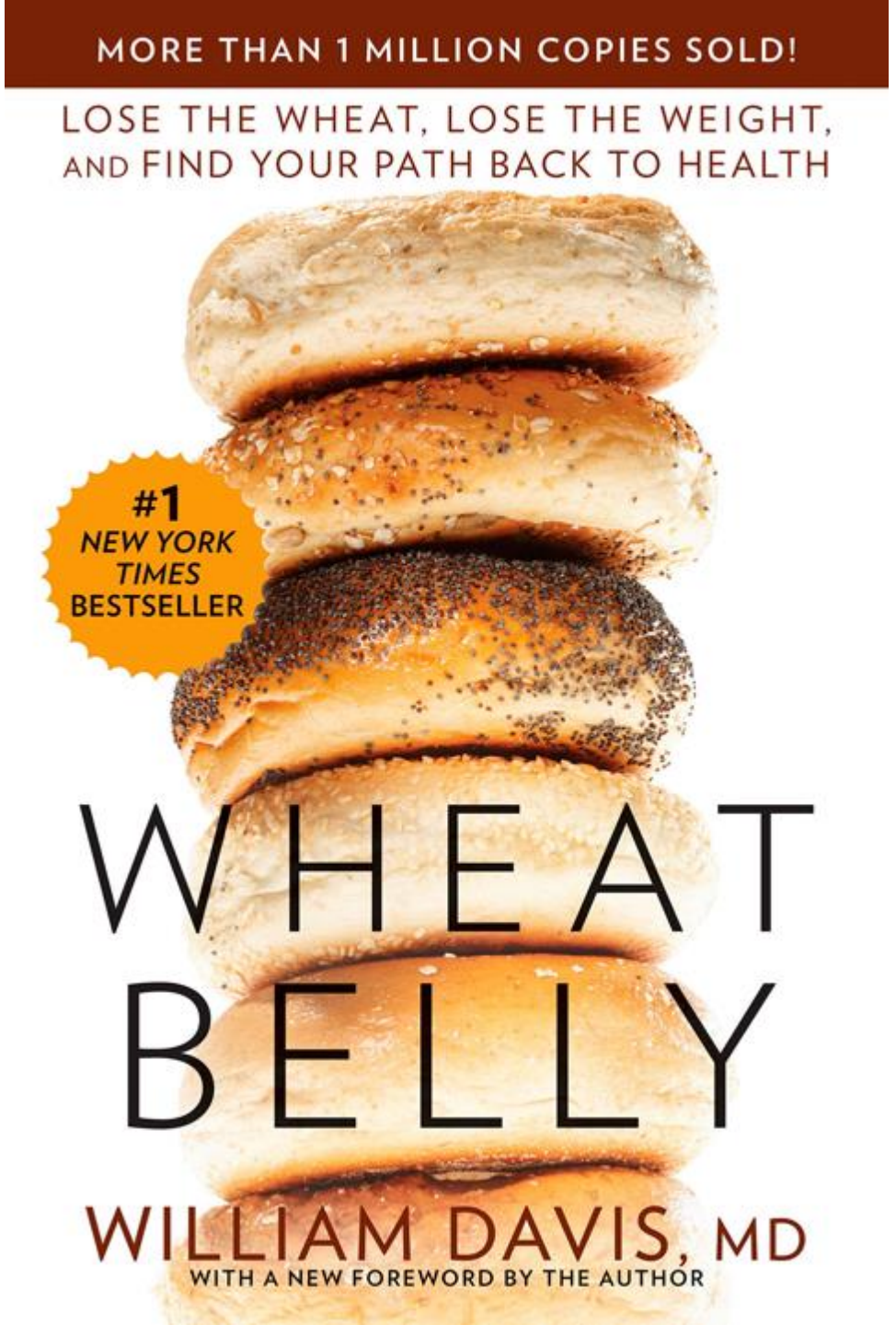


Bonder et al. Genome Med. 2016;8:45

Cladogram showing the differentially abundant taxa

Going gluten free

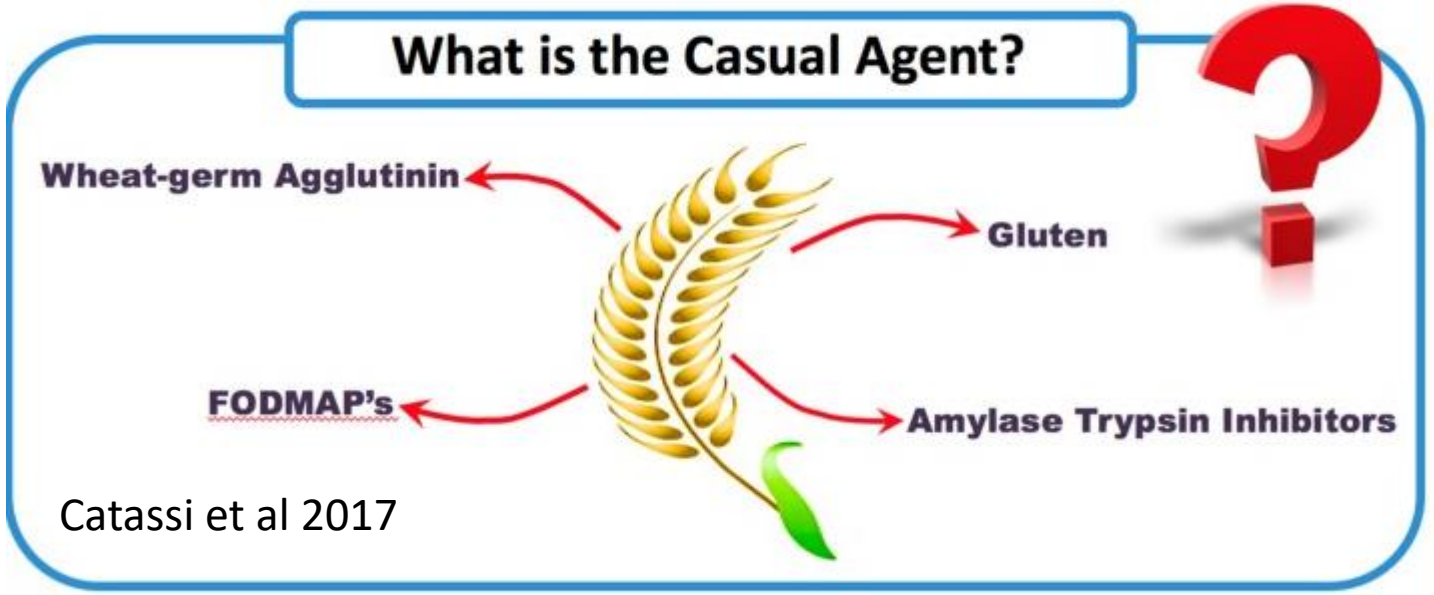
- Certainly not a ‘healthy’ diet, despite public perception!
- Linked in scientific literature with:
  - Higher cost
  - Inconvenience
  - Micronutrient deficiencies
  - Heavy metal exposure (arsenic)
  - Weight gain (not weight loss!)
  - Metabolic syndrome



Raehsler et al. Clin Gastroenterol Hepatol. 2018;16:244-251

Self reported gluten sensitivity

- Patients without celiac disease who associate adverse physiological symptoms (gastrointestinal or extra-intestinal) with the ingestion of wheat or gluten
- Self diagnosis!
- Causes? A real disease?



Catassi et al 2017

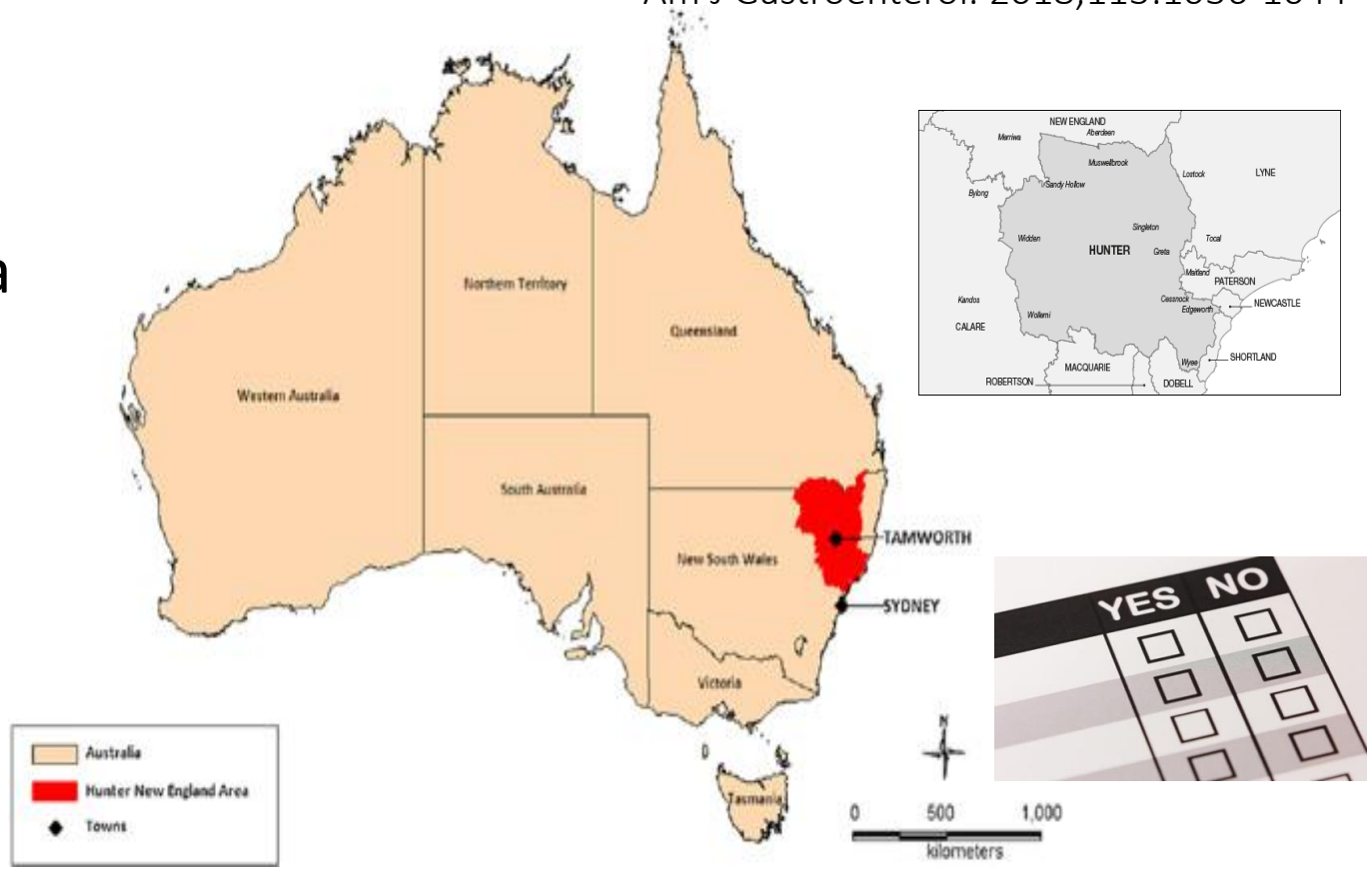
see related editorial on page x

Wheat Intolerance and Chronic Gastrointestinal Symptoms in an Australian Population-based Study: Association Between Wheat Sensitivity, Celiac Disease and Functional Gastrointestinal Disorders

Michael D. E. Potter, MBBS (Hons)[1,2], Marjorie M. Walker, BMedSci, BMBS, FRCPath, FRCPA[1,2], Michael P. Jones, PhD[1,2,3], Natasha A. Koloski, BA (Hons), PhD[1,2,4,5], Simon Keely, PhD[1,2] and Nicholas J. Talley, MD, PhD, FRACP[1,2]

Am J Gastroenterol. 2018;113:1036-1044

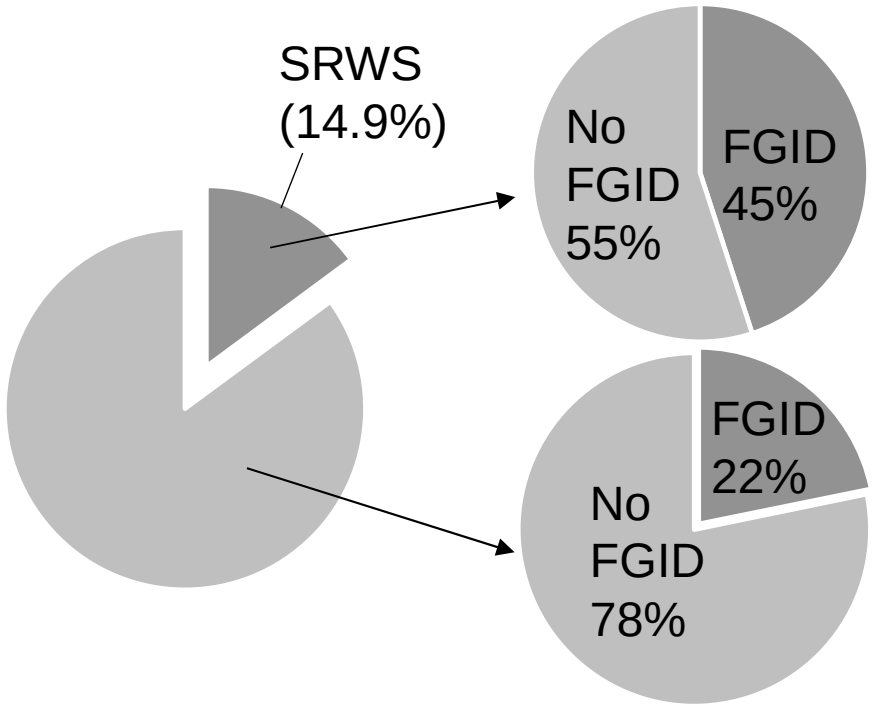
- Participants (n=8499) randomly selected from the electoral rolls
- Hunter area (n=7499) (Charlton, Newcastle & Shortland); Gosford area (n=1000) (Dobell and Robertson)
- Self reported conditions (coeliac, IBD, allergy, diabetes)
- Kessler 6; assesses psychological distress
- Lifestyle factors (BMI, smoking)
- Demographics (age, gender)
- Rome III questions (IBS, FD)



Prevalence of self-report wheat sensitivity (SR-NCGS) and functional GI disorder (FGID)

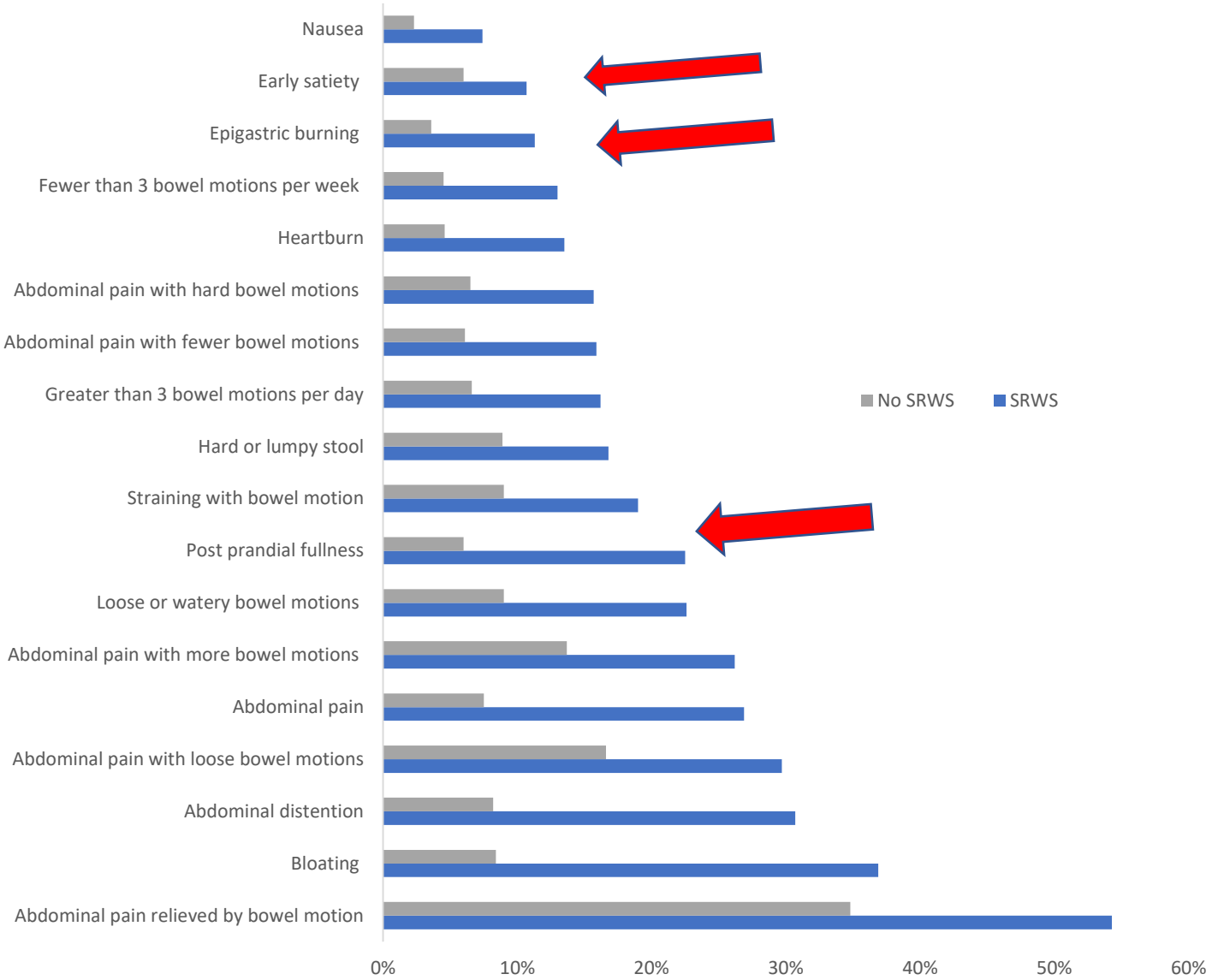
- Approximately 14.9% of the population self-report wheat sensitivity (SRWS)

- In those with SRWS, almost half (45%) fulfil criteria for a functional GI disorder (FGID), compared with only 22% of those without SRWS



Symptoms associated with self-reported wheat sensitivity (SR-NCGS)

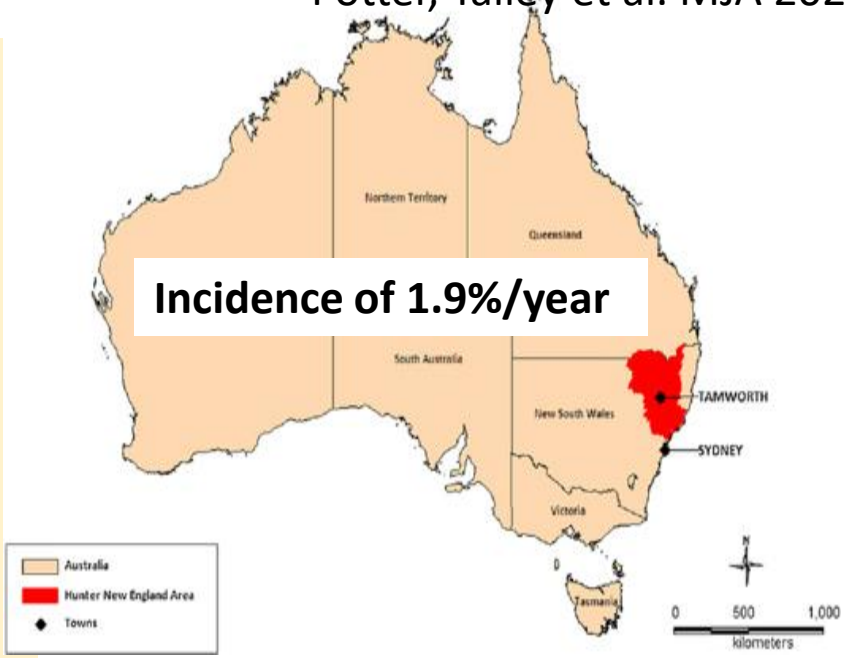
- All symptoms associated
- IBS-like symptoms common
- Functional dyspepsia (FD) symptoms (e.g. early satiety, postprandial fullness, epigastric burning) reported in significantly higher frequency by SRWS



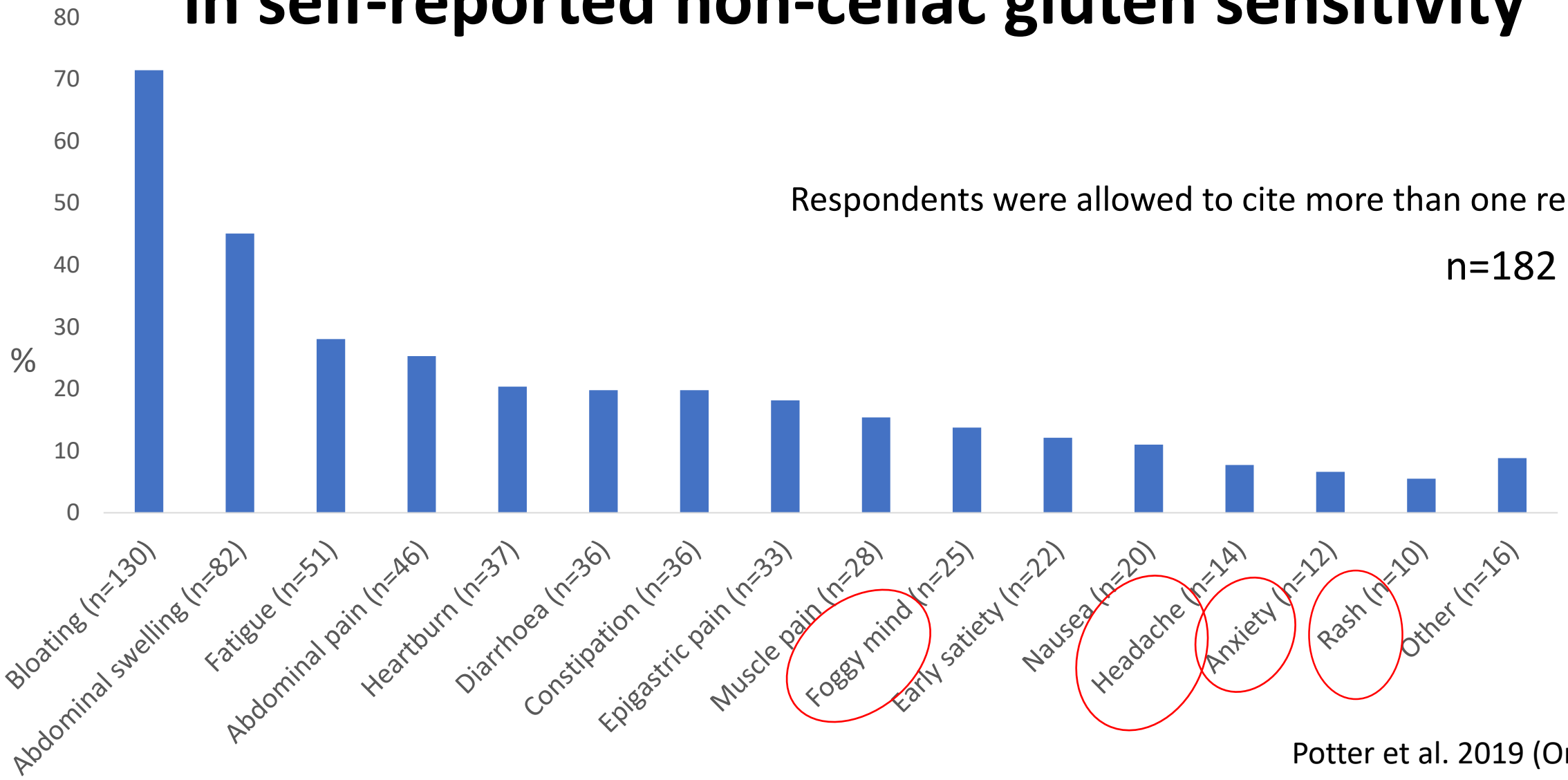
Incidence of self reported non-celiac gluten sensitivity (SR-NCGS)

Potter, Talley et al. MJA 2020

- A random population sample of consenting participants surveyed in 2015 and 2018
- Validated outpatient questionnaire
- SR-NCWS defined as those who reported adverse symptoms with gluten or wheat ingestion without another GI diagnosis
- 1322 participants approached returned a completed survey (response rate 60.5%)
- Prevalence of SR-NCGS in 2015 13.8%, and in 2018 13.9% (p=0.8)
- 5.5% developed new onset SR-NCWS, an incidence of 1.9%/year
- Incident SR-NCGS associated with a physician diagnosis of functional dyspepsia (OR=1.76) p=0.05
- Male sex and older age protective against new onset SR-NCGS
- No other studies on incidence to compare findings



Adverse symptoms reported with wheat ingestion in self-reported non-celiac gluten sensitivity



Respondents were allowed to cite more than one reason

n=182

Potter et al. 2019 (Oral, DDW)

Global prevalence NCGS

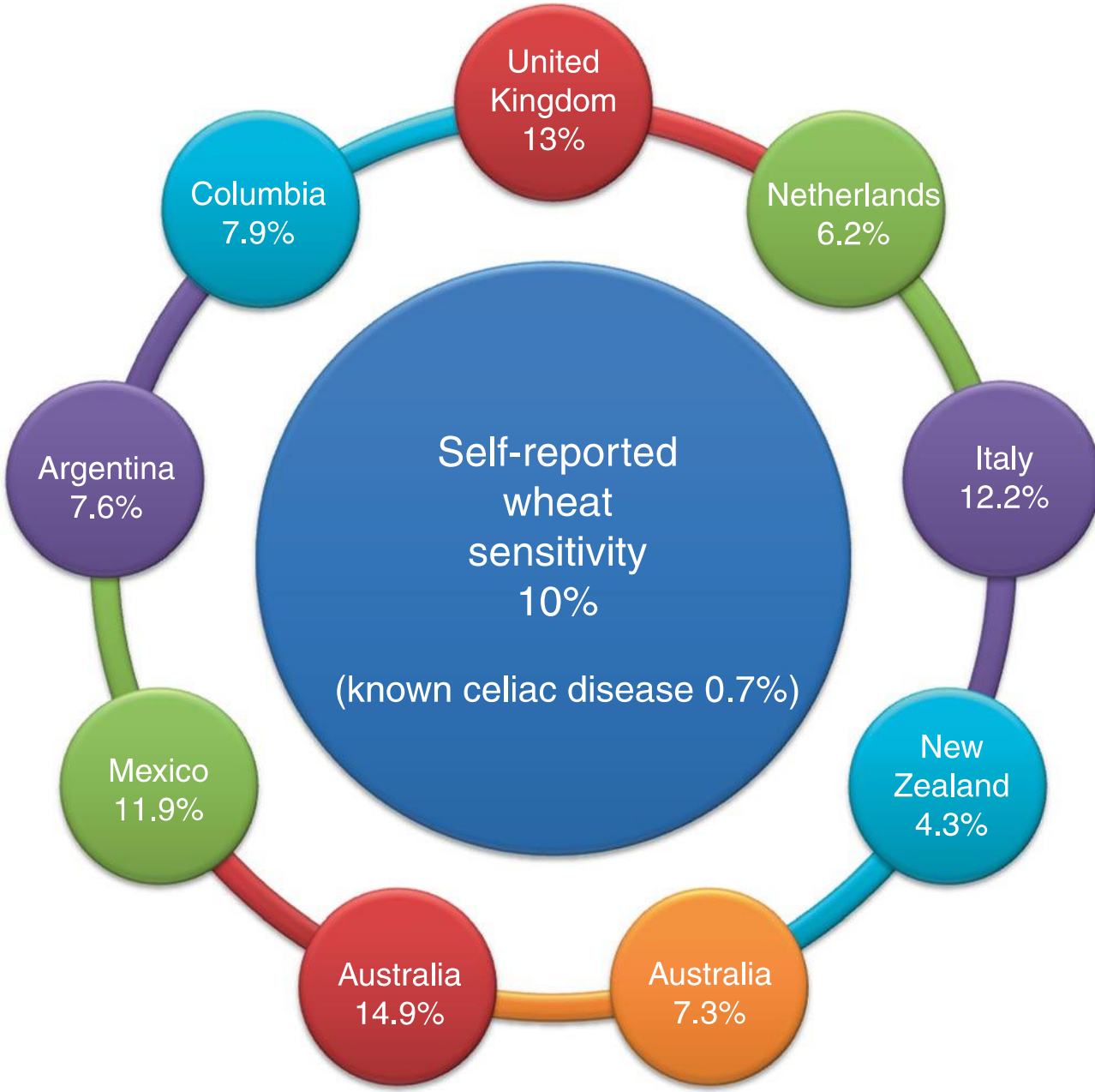
- These figures similar to other international studies
- Range 4-15%
- Pooled prevalence ~10%

Are these people truly sensitive to wheat?

Extra-intestinal symptoms conspicuous

A new" disease?

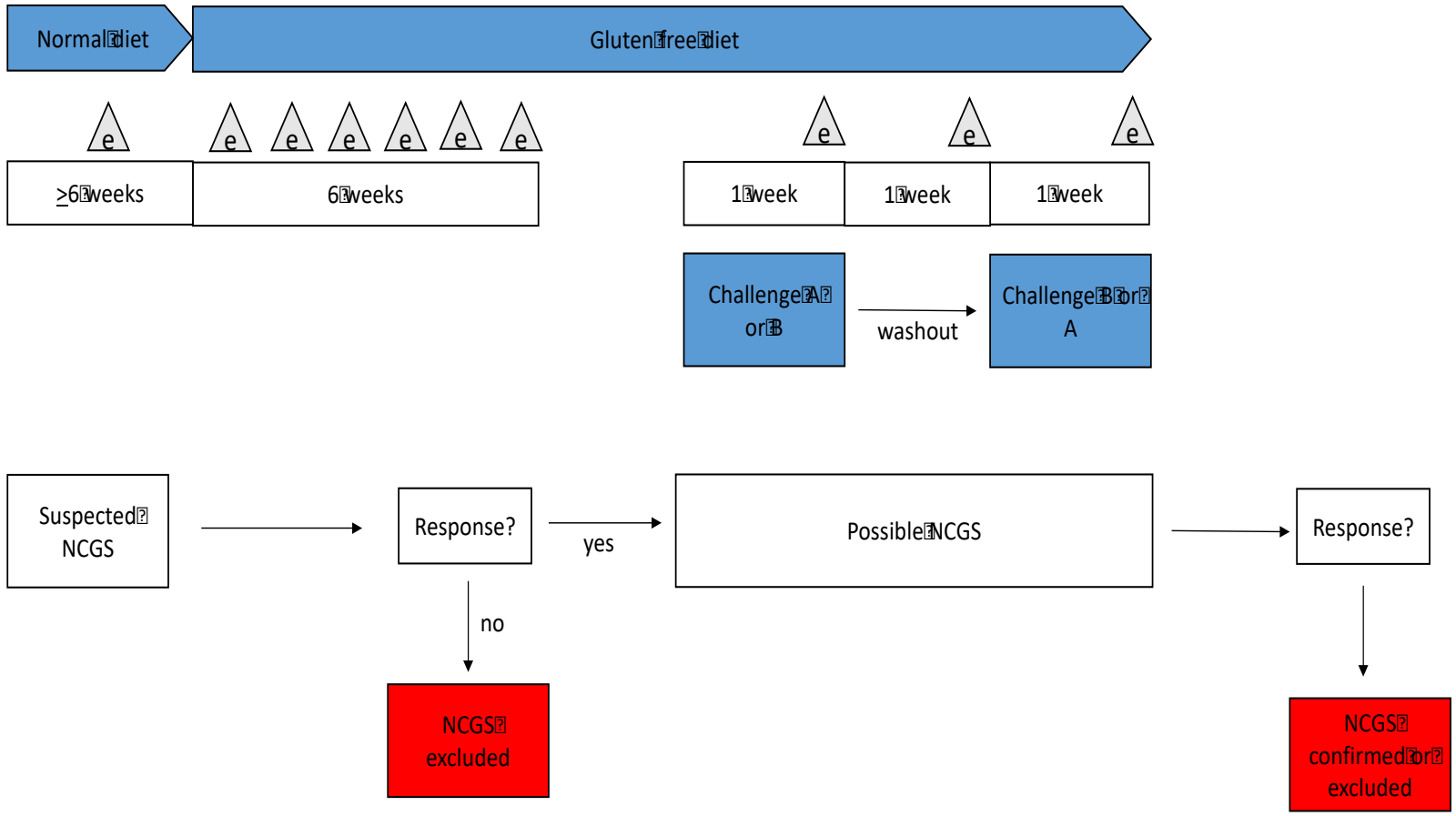
Is the gluten free diet a healthy alternative?



Aziz, Am J Gastroenterol. 2018;113:945-8.

Non-celiac gluten sensitivity: a stricter definition

- The ‘Salerno consensus criteria’
- Requires double blind placebo controlled dietary trial



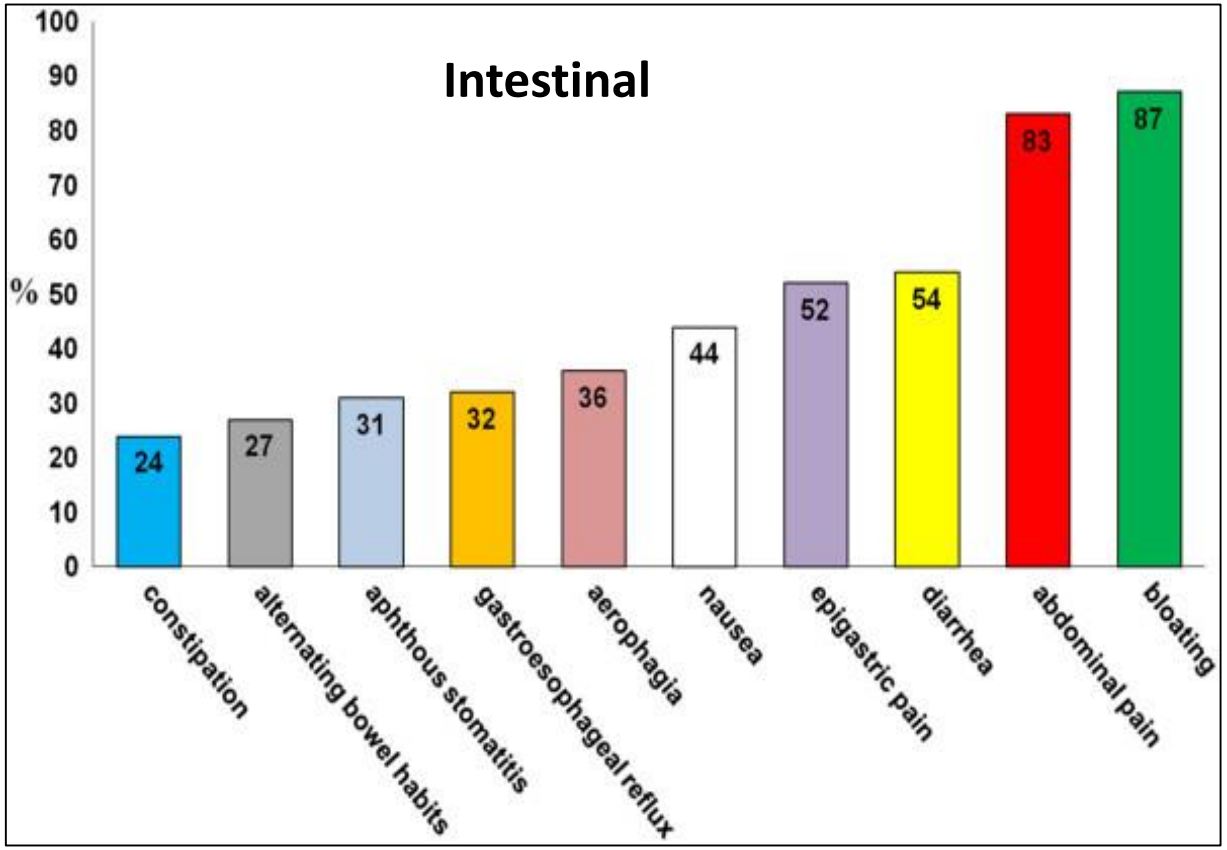
Catassi et al. 2015. Nutrients;7(6):4966-77

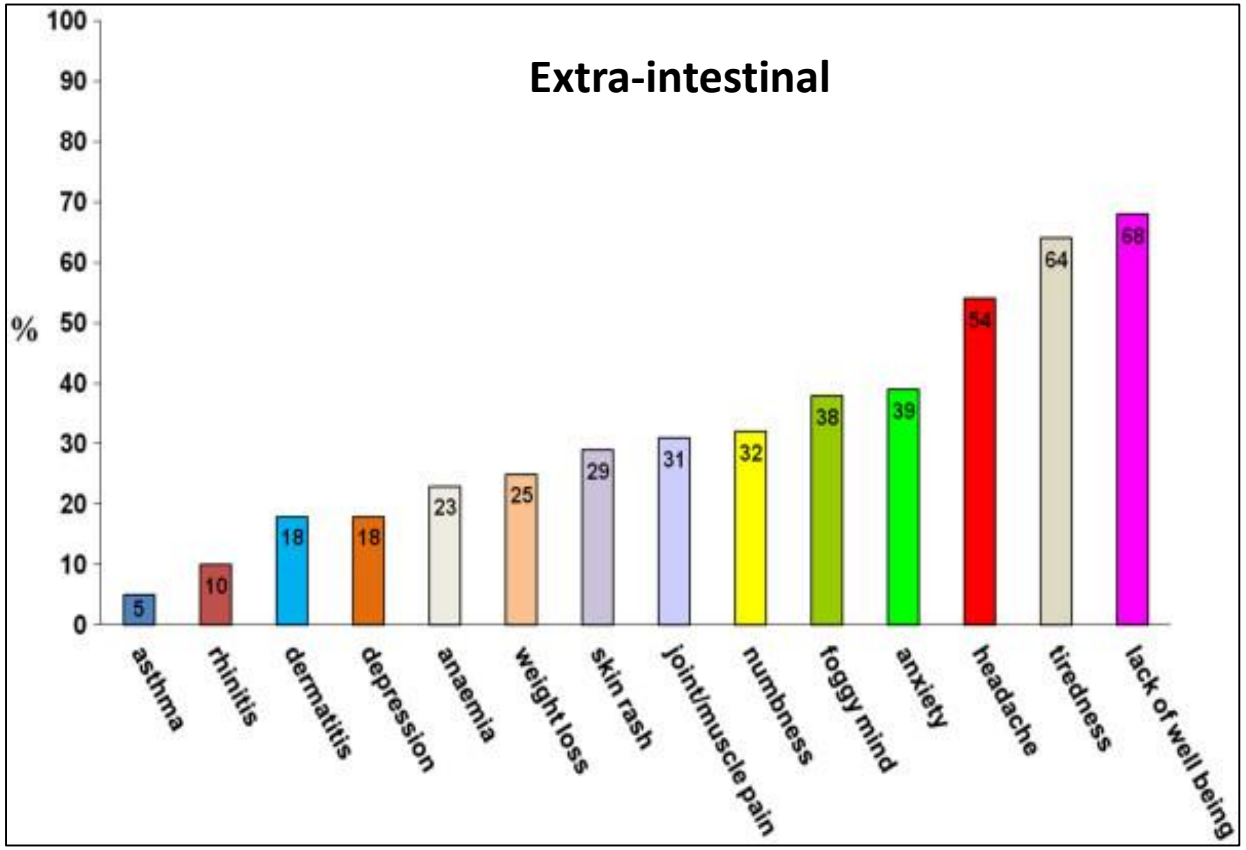
Potter et al. 2017. MJA;207(5):211-215

Clinical features of “confirmed” non-celiac gluten sensitivity

- Prospective survey 486 patients with NCGS made by dietary re-challenge trials

  Note similar to self reported NCGS, and to IBS and/or functional dyspepsia!





Volta et al. BMC Med. 2014;12:85.

Is NCGS a valid diagnosis?

- Current consensus criteria allows for 24 possible symptoms to be associated
- *Extra-intestinal symptoms presumed to differentiate NCGS from FGIDs*
- **This doesn't all seem plausible**

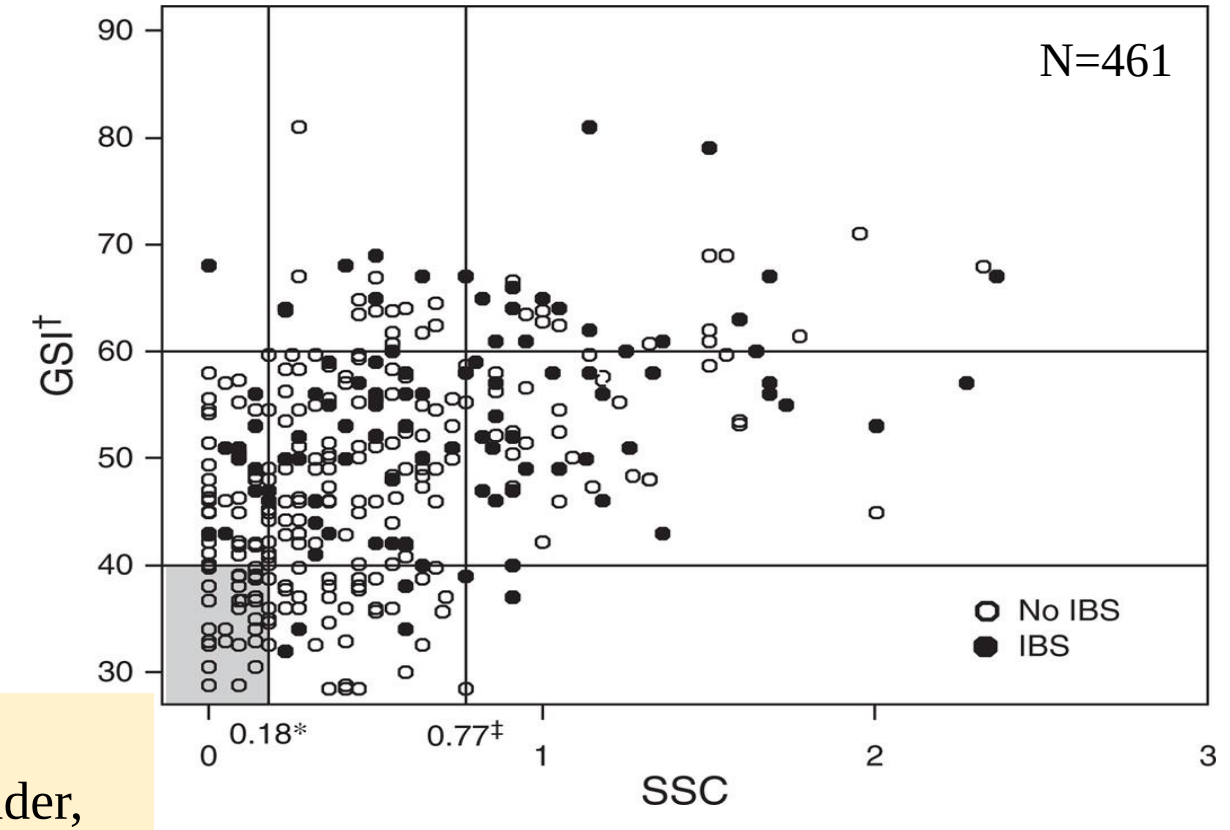
Catassi 2015 Nutrients
Volta et al. Gastoenterol Clin Nth Am 2019

Intestinal Symptoms
Abdominal pain or discomfort
Heartburn
Acid regurgitation
Bloating
Nausea and vomiting
Borborygmus
Abdominal distension
Eructation
Increased flatus
Decreased passage of stools
Increased passage of stools
Loose stools
Hard stools
Urgent need for defecation
Feeling of incomplete evacuation
Extra-intestinal symptoms
Dermatitis
Headache
Foggy mind
Fatigue
Numbness of the limbs
Joint/muscle pains
Fainting
Oral/tongue lesions
Other (specify)

Is it true extra-intestinal symptoms in NCGS identify a unique disease? No! Look at IBS…

SSC items	IBS (*n*=106)	Non-IBS (*n*=355)
Overall SSC score	0.7±0.5	0.5±0.5
Headache	1.3±1.0	0.7±0.9
Backache	1.2±1.1	0.9±1.2
Asthma	0.1±0.6	0.1±0.5
Insomnia	1.0±1.2	0.7±1.1
High blood pressure	0.2±0.6	0.2±0.6
Fatigue	1.4±1.2	0.9±1.1
General stiffness	1.1±1.2	0.9±1.2
Heart palpitations	0.3±0.6	0.2±0.6
Eye pain	0.4±1.0	0.2±0.6
Dizziness	0.5±0.9	0.4±0.9
Weakness	0.3±0.7	0.3±0.9

Distribution of the subjects with IBS according to the somatic symptom checklist (SSC) and GSI scores of the SCL-90-R



In a population-based study, somatic symptoms were significantly associated with IBS independent of age, gender, education level, marital status, smoking, alcohol use, and BMI

Choung, Talley et al. Am J Gastro 2009;104:1772-9

How many self-reporters have “true” NCGS?

- Not many!
- <1 in 5 “true” NCGS
- 2 in 5 respond to placebo!

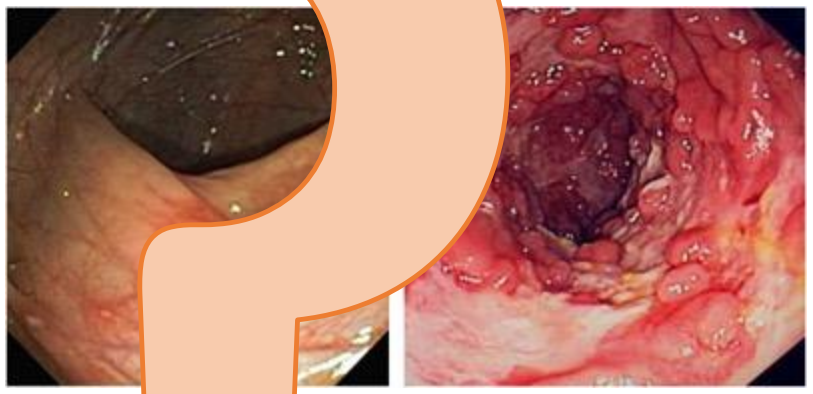
Molina-Infante. CGH 2017;15:339-348

	Outcome report after placebo-controlled gluten challenge			
	Quantitative	Qualitative		
		Gluten-specific symptoms (symptoms triggered with gluten but not with placebo)	Nocebo effect (similar or higher symptoms with placebo compared with gluten)	No symptoms with either gluten or placebo
Biesiekierski et al,[17] 2013, Australia	Similar symptom worsening with gluten or whey protein diet	3 of 37 (8%)	11 of 37 (29%)	NR
Di Sabatino et al,[20] 2015, Italy	Significant symptom worsening with gluten compared with placebo (56.9 vs 43.7; $P = .034$)	9 of 61 (15%)	52 of 61 (85%)	NR
Zanini et al,[21] 2015, Italy	NR	12 of 35 (34%)	17 of 35 (49%)[a]	6 of 35 (17%)
Elli et al,[22] 2016, Italy	Borderline significant symptom worsening with gluten vs placebo (6.1 vs 5.3; $P = .05$)	14 of 98 (14%)	14 of 98 (14%)	70 of 98 (71%)
Picarelli et al,[23] 2016, Italy	Nonsignificant symptom worsening with gluten vs placebo (61% vs 46%; $P = .6$)	NR	NR	NR
Overall results		38 of 231 (16%)	94 of 231 (40%)	76 of 133 (57%)

Is NCGS a valid diagnosis? Reframe the question

Potter MDE, Walker MM, Keely S, Talley NJ. Gut. 2018;67:2073-2077

IBS

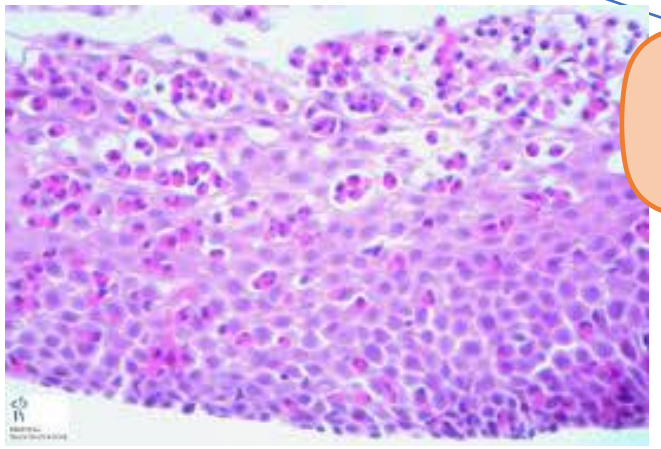


IBD

Does gluten or wheat *cause* GI disease?
How does this fit into the framework of already defined illnesses

- Functional GI disorders
  - Irritable bowel syndrome
  - Functional dyspepsia
- Inflammatory bowel diseases
- Eosinophilic GI diseases
- Others?

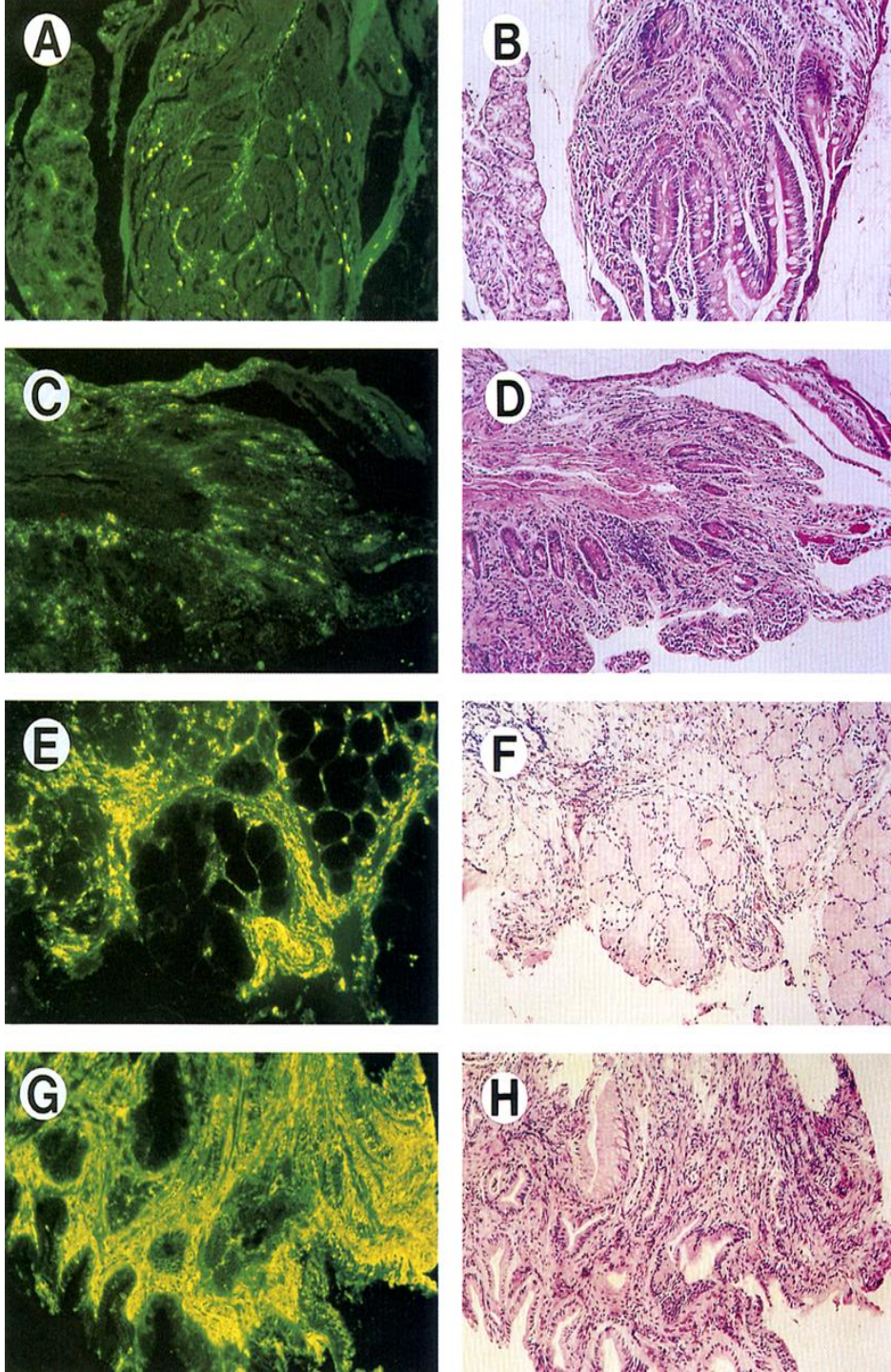
EoE



FD

A biomarker? Increased eosinophils in celiac disease

- Degrees of eosinophil infiltration and eosinophil degranulation, as evidenced by localization of the eosinophil granule major basic protein (MBP), compared using specific indirect immunofluorescence Formalin-fixed, paraffin-embedded biopsy specimens from 11 patients with eosinophilic gastroenteritis, 4 patients with celiac disease, and 18 healthy asymptomatic volunteers
- In small intestine, **both eosinophil infiltration and extracellular MBP deposition scores** significantly greater in eosinophilic gastroenteritis and **celiac disease** vs. controls

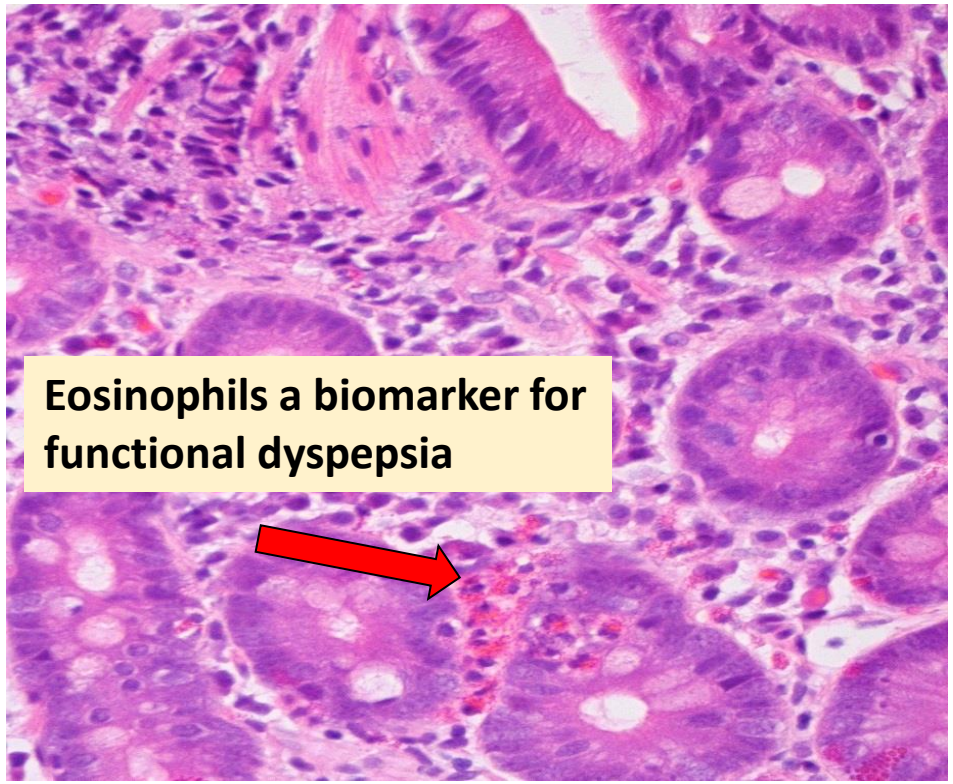


Talley NJ et al. Gastroenterology. 1992;103(1):137-45.

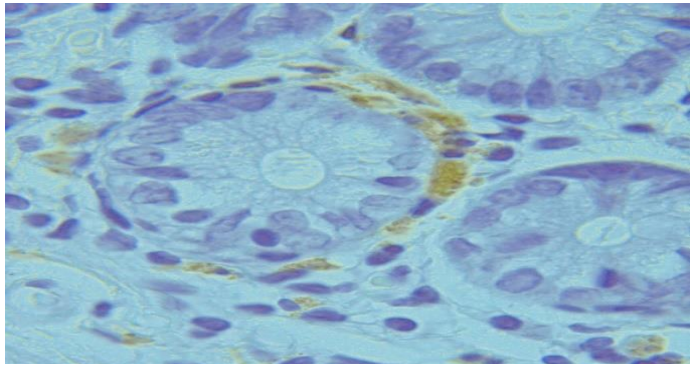
Nonulcer Dyspepsia and Duodenal Eosinophilia: An Adult Endoscopic Population-Based Case-Control Study

Clin Gastroenterol Hepatol. 2007 5:1175-83

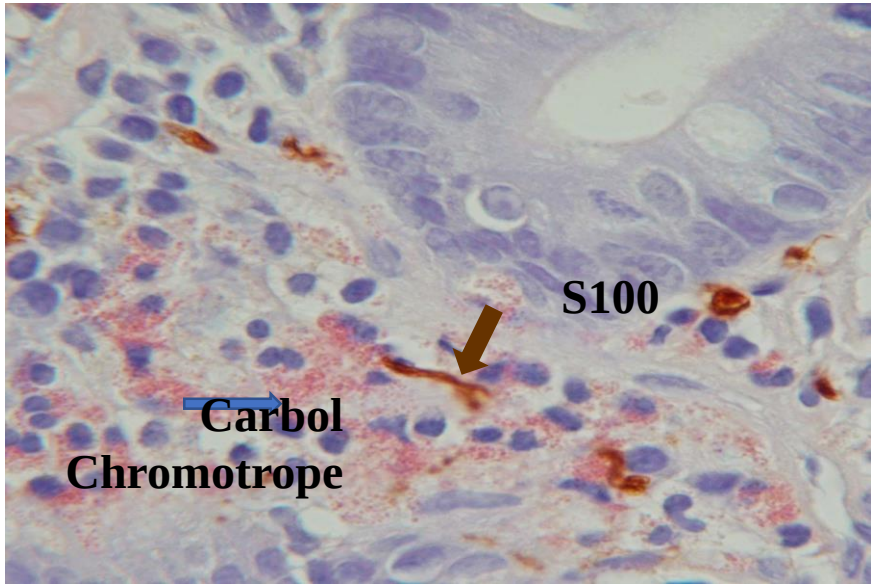
NICHOLAS J. TALLEY,*,‡ MARJORIE M. WALKER,§ PERTTI ARO,‖ JUKKA RONKAINEN,‖ TOM STORSKRUBB,‖ LAURA A. HINDLEY,§ W. SCOTT HARMSEN,¶ ALAN R. ZINSMEISTER,¶ and LARS AGRÉUS‖



Clusters of eosinophils in D1 observed in 26 FD (51%) vs. 10 controls (21%) (p=0.003)

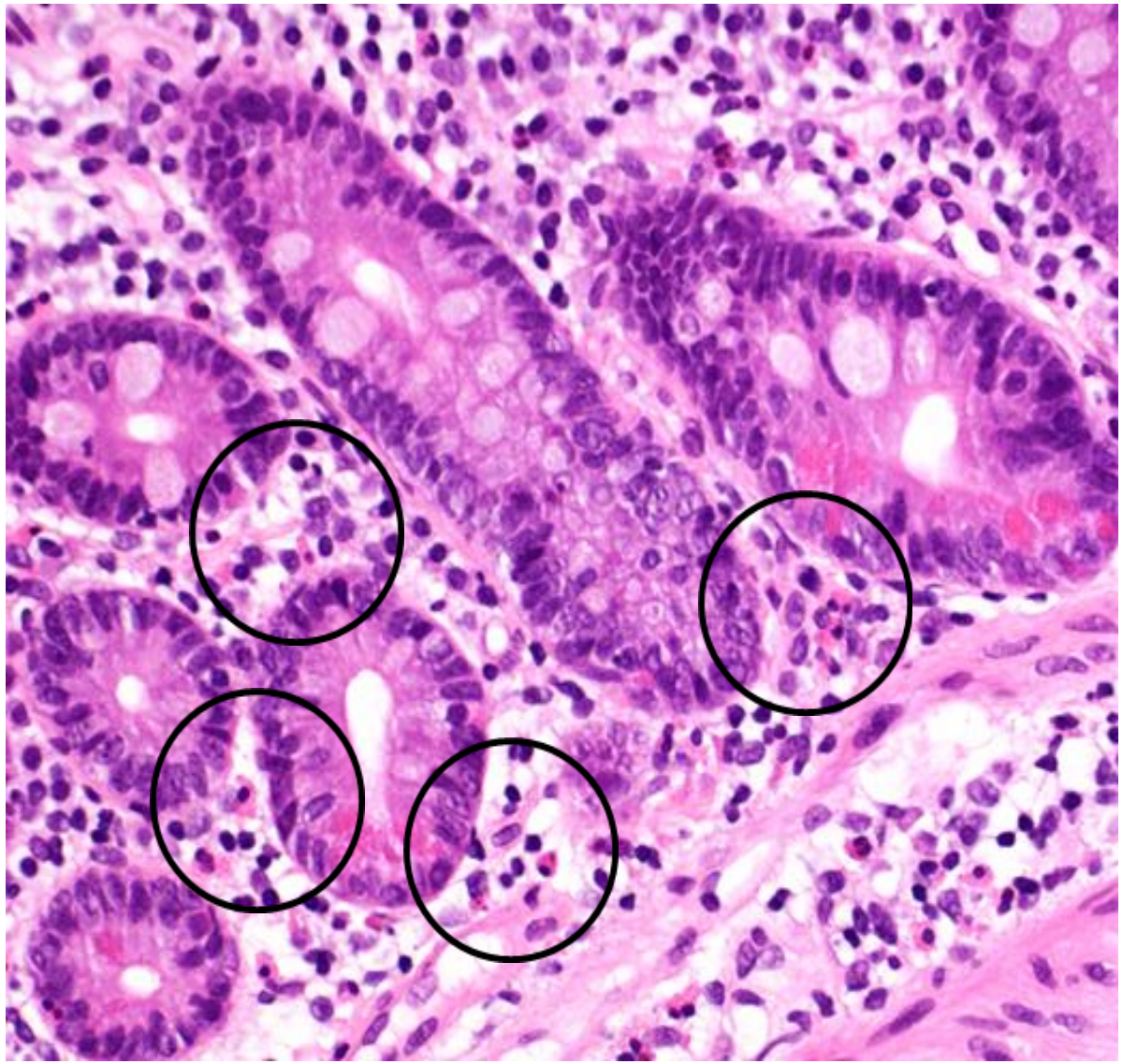


MBP – degranulation in FD



PDS <u>not</u> EPS linked to duodenal eosinophils

Eosinophils a biomarker for NCGS?

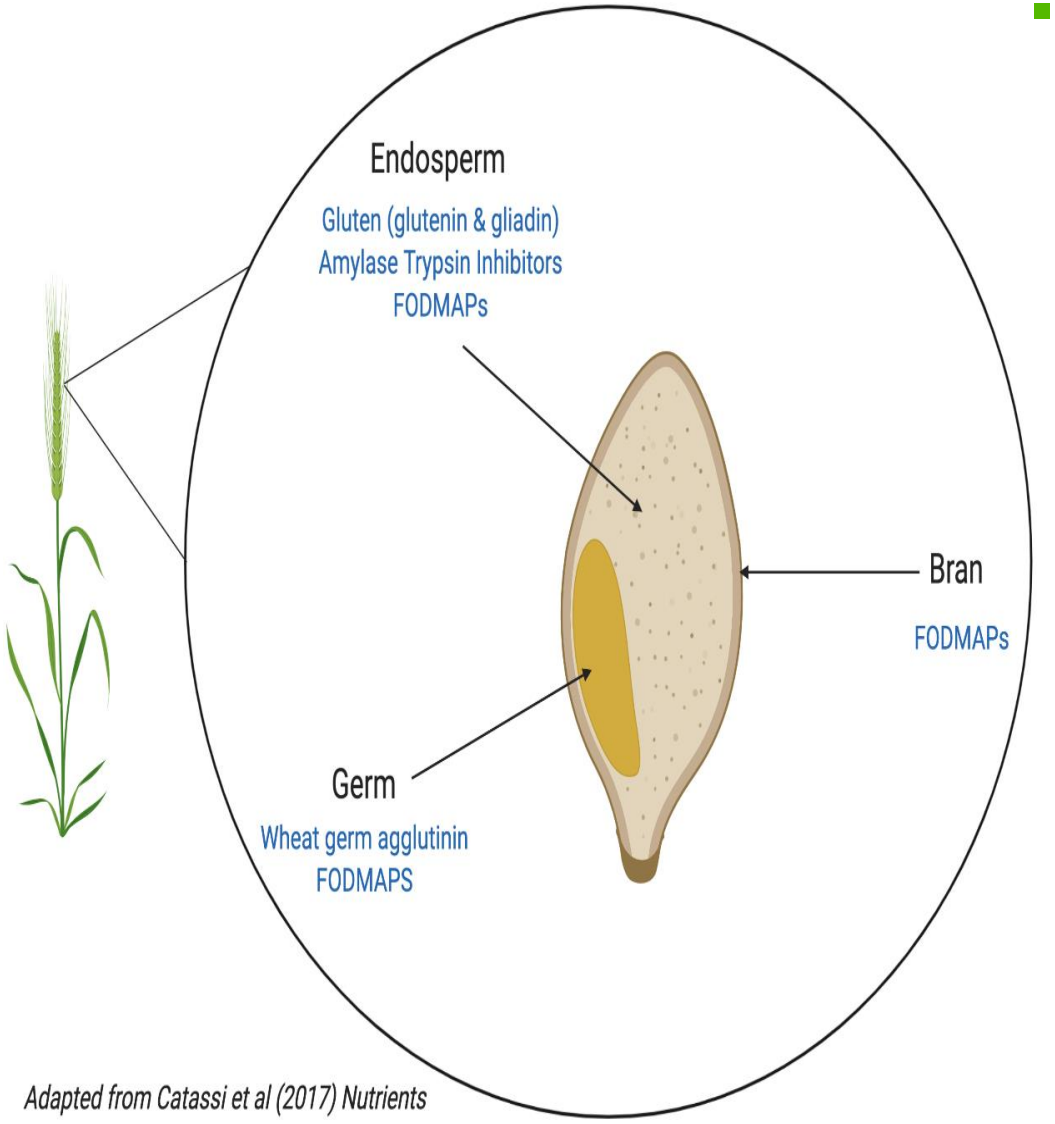


Duodenal eosinophilia (circled) in NCWS
Increased rectal eosinophils also observed
Diagnosis by double-blind wheat challenge

Carroccio *et al* Am J Gastroenterol 2012; 107:1898–1906
Carroccio et al. Clin Gastroenterol Hep 2018 in press

- ?Innate immune system involvement
  - Increased intestinal permeability
  - Interferon gamma expression
  - Epithelial cell damage
  - Duodenal (and rectal) eosinophilia

Immunogenicity of wheat

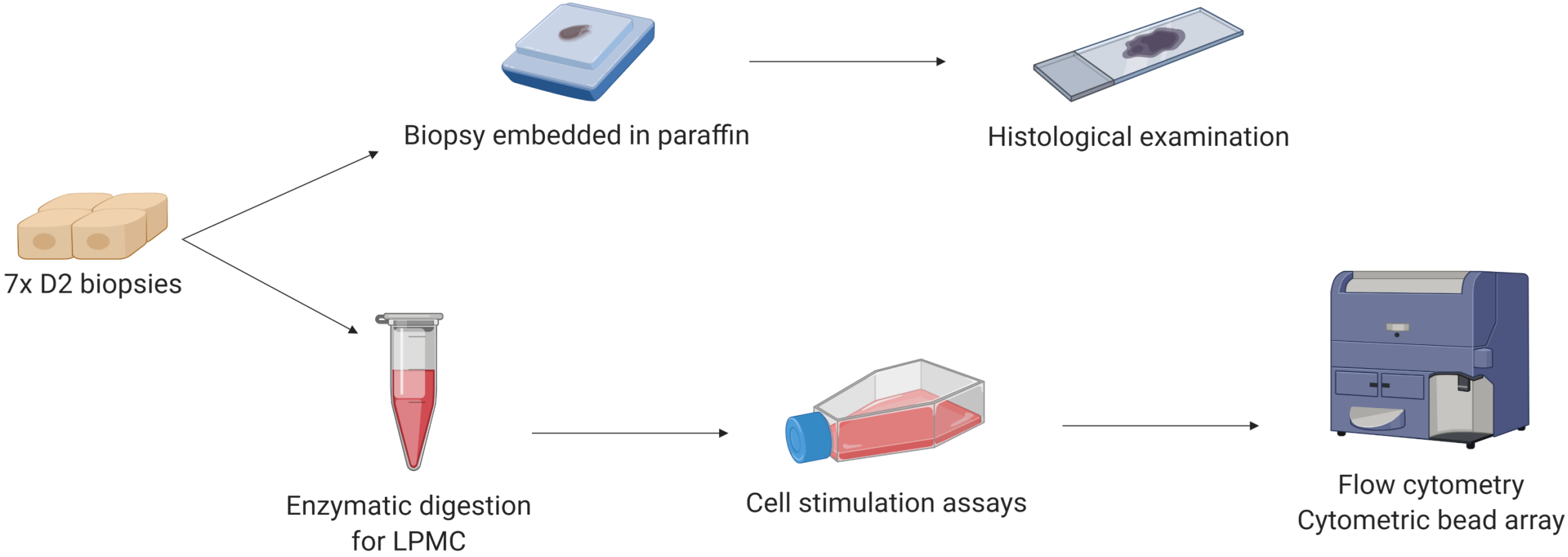


Adapted from Catassi et al (2017) Nutrients

- **Wheat contains:**
  - Gluten:
    - Protein complex of glutenins and gliadin proteins
    - Over 50 epitopes identified in gliadin
    - Specific epitopes of gliadin initiate immune response in coeliac disease

      Ciccocioppo et al (2005) Clin Exp Immunol.
  - FODMAPs
  - Amylase trypsin inhibitors
  - Wheat germ agglutinin

To examine whether antigens present in gluten or gliadin provoke an immune response from duodenal mononuclear cells isolated from FD

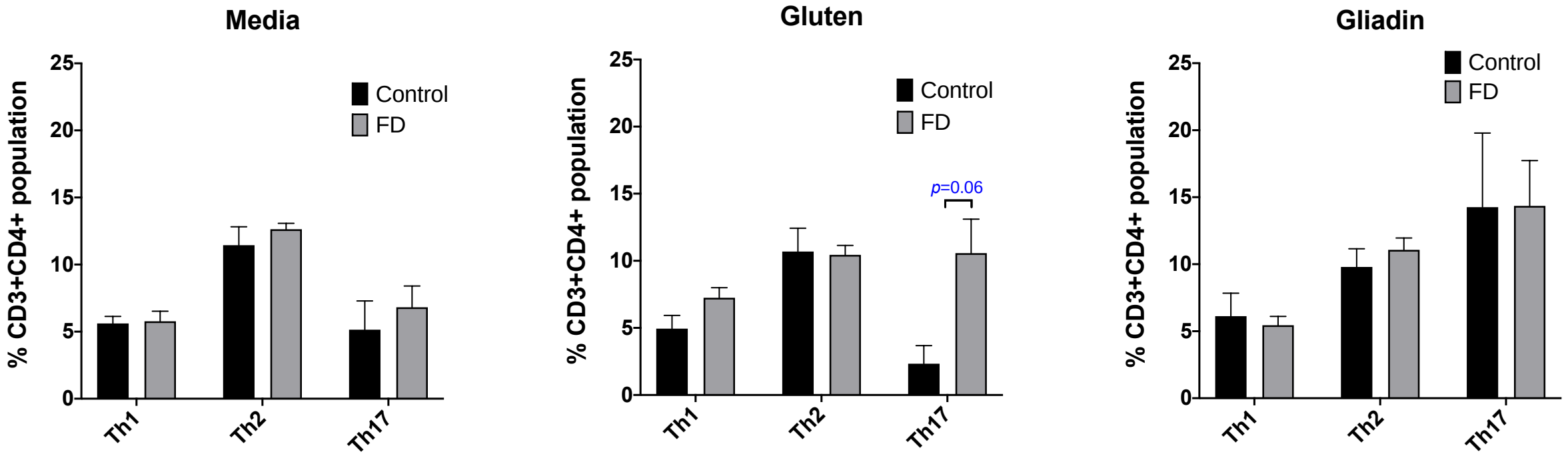


A subset of FD patients have immune responses to gluten and gluten associated proteins that may be responsible for their symptoms?

LPMC: Lamina propria mononuclear cells - both innate and adaptive cells

Gluten stimulation increases Th17+ CD4+ lymphocytes in LPMC

Cells treated with 1mg/mL gluten/gliadin, incubated for 24hours

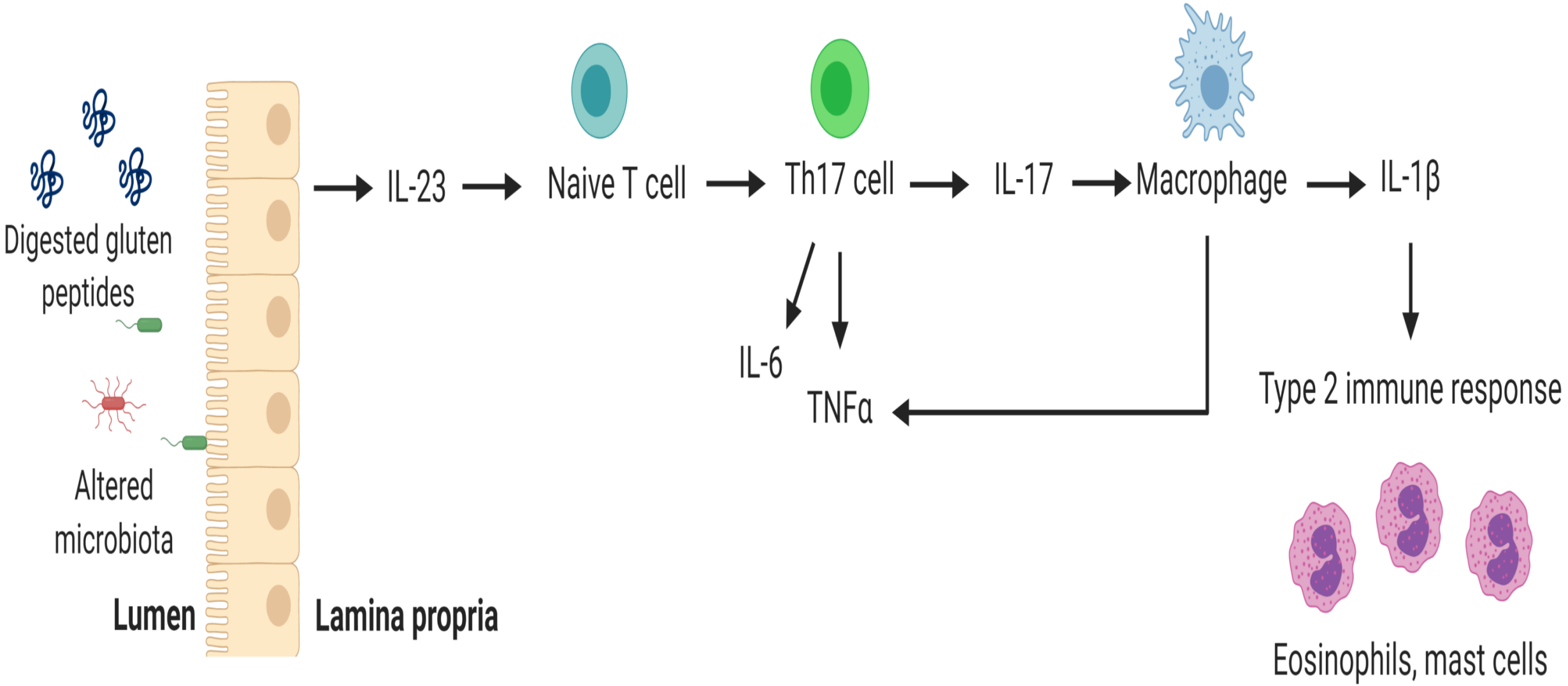


An adaptive response is seen in response to gluten, but not gliadin, in FD patients

Stimulation of LPMC cells with **gluten** drives an increase in **Th17 lymphocytes**

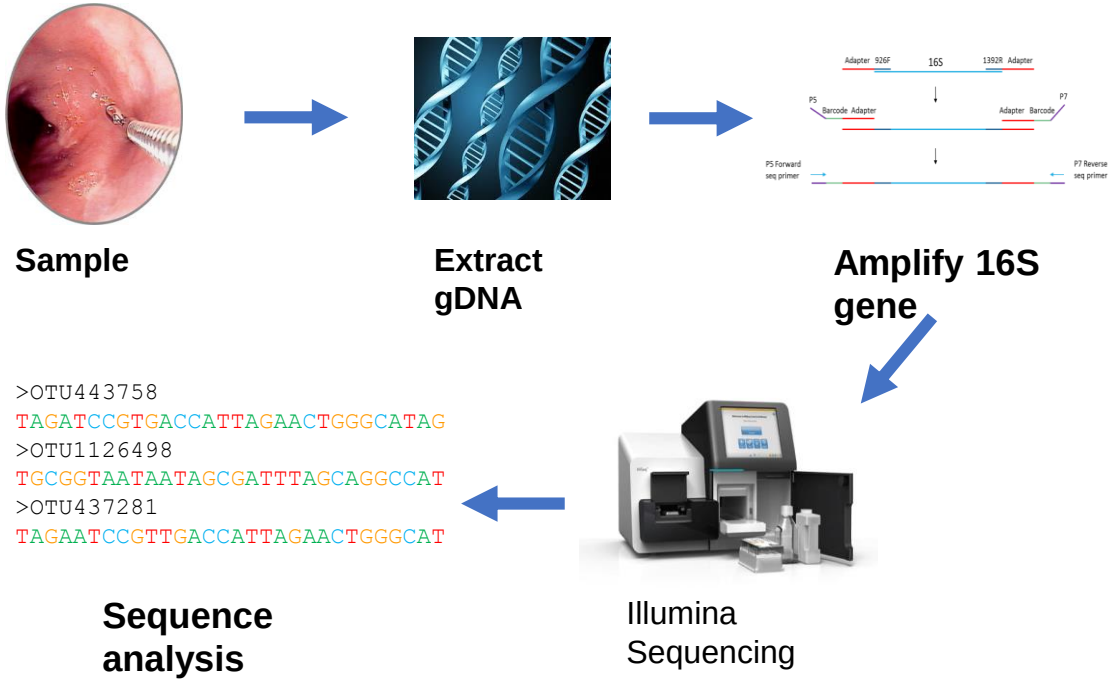
Indirect evidence for Th17 involvement in FD (macrophages, TNF, IL-1β, IL-6)

Hypothesised Th17 mechanism in FD and IBS linked to wheat



Immune activation/duodenal biome changes in FD: Is immune activation the explanation for NCWS?

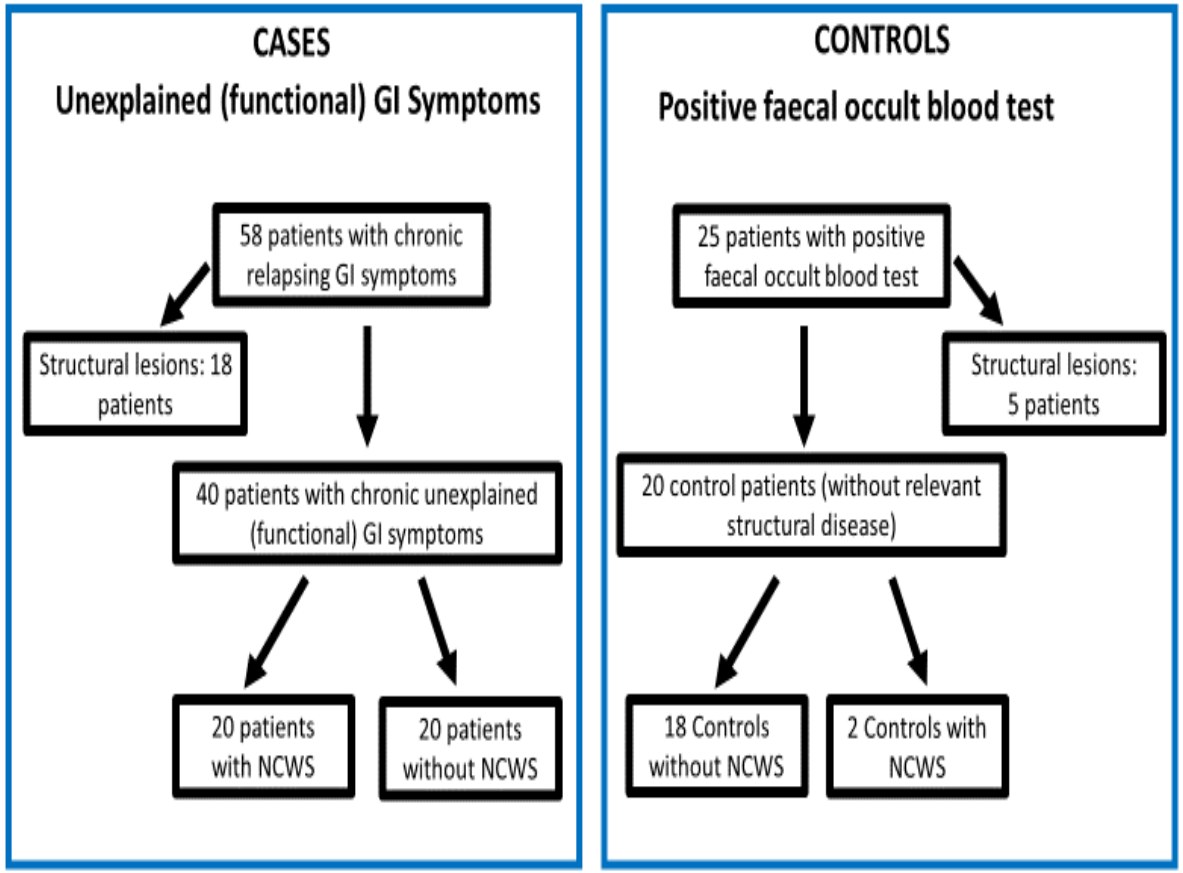
- **58 patients** referred for diagnostic work-up and treatment of **chronic or relapsing GI symptoms**
- **Control patients** with **a positive fecal occult blood test or iron deficiency**
- **All patients** underwent **routine diagnostic work-up** including upper GI endoscopy
- Patients with relevant **symptoms suggesting colonic disease** also underwent a **colonoscopy**
- **Structured interview: wheat sensitive** (NCWS +)

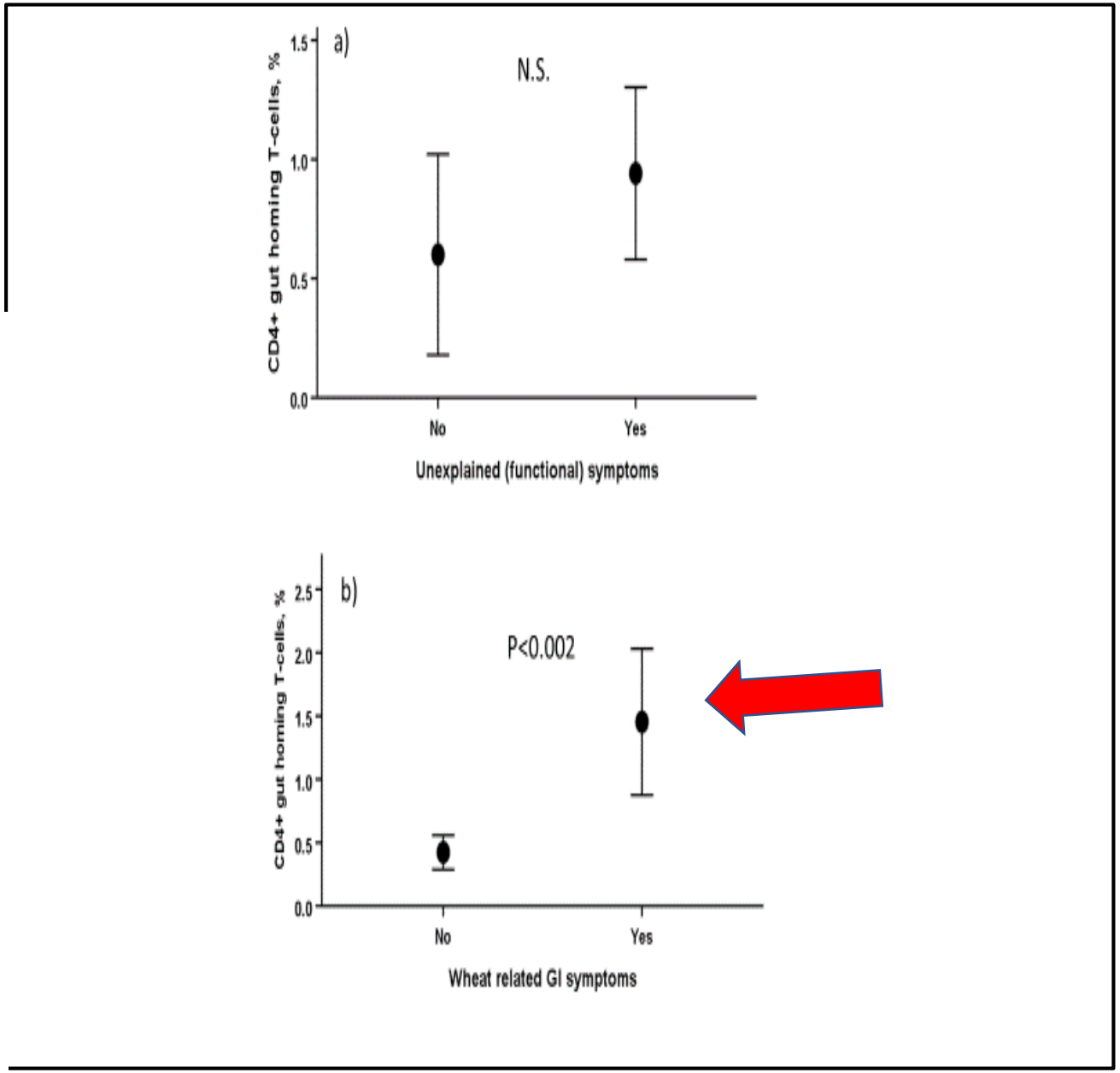


- During **endoscopy, mucosal samples were collected in the 2nd part of the duodenum** utilising the Brisbane aseptic biopsy forceps for microbiome
- **Nutrient challenge:** Standardised (non-gluten) nutrient challenge performed to assess GI sensory function

➢ **Immune function:** Peripheral blood mononuclear cells (PBMCs) were isolated by density centrifugation and CD4 + α4 β7 + CCR9 +T cells quantified by flow cytometry

FGIDs and wheat sensitivity: increased gut homing T cells

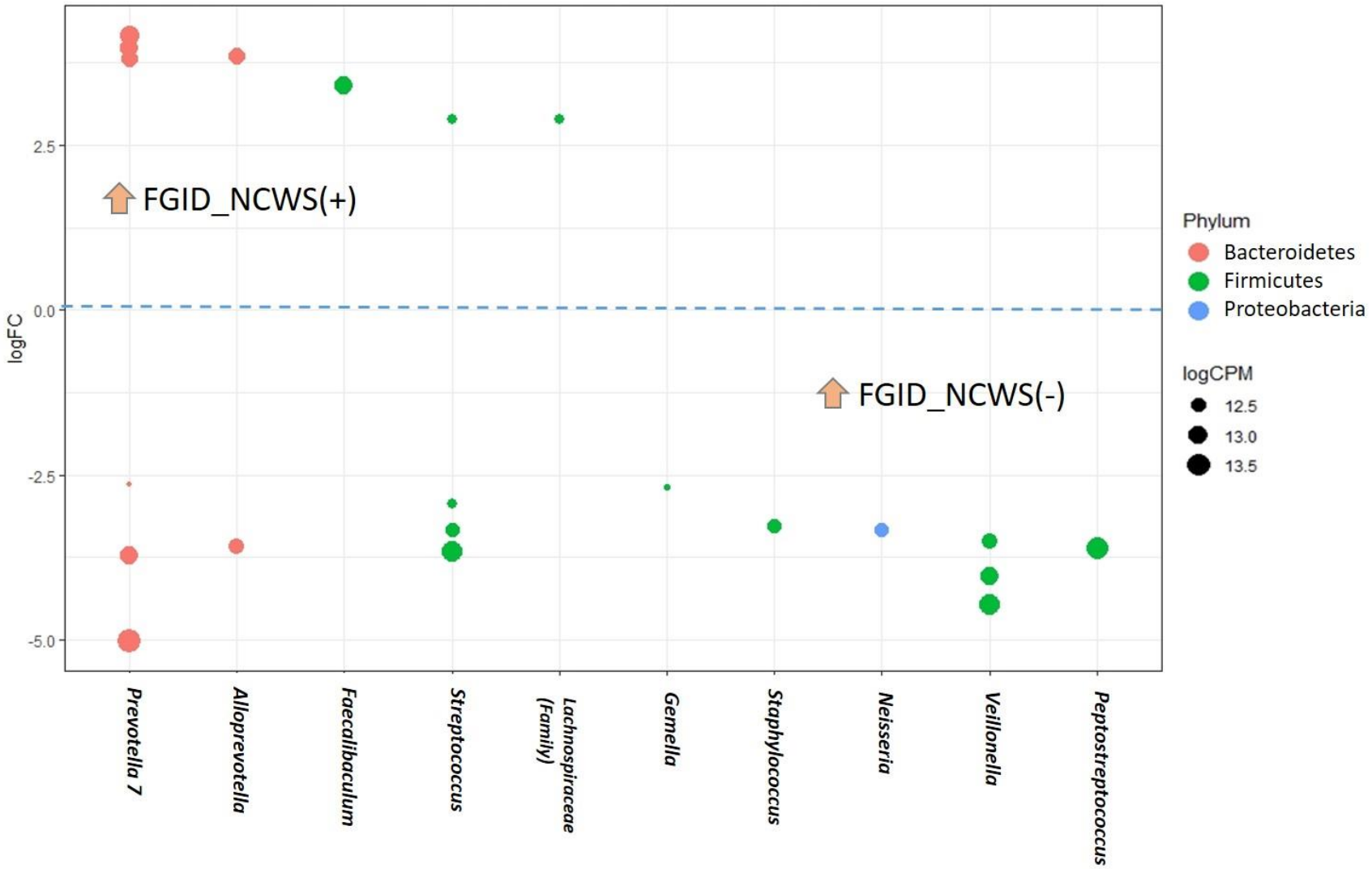




FGIDs and wheat sensitivity: duodenal MAM

- EdgeR analysis of the d-MAM profiles identified
  11 bacterial taxa that were discriminatory (FDR <0.001) between the control and FGID patient groups without NCWS; and 21 bacterial taxa between FGID patients with or without NCWS
- in FGID_NCWS(+) patients, there is a displacement of *Peptostreptococcus, Veillonella* and *Streptococcus* spp. and in particular, by *Faecalibaculum*

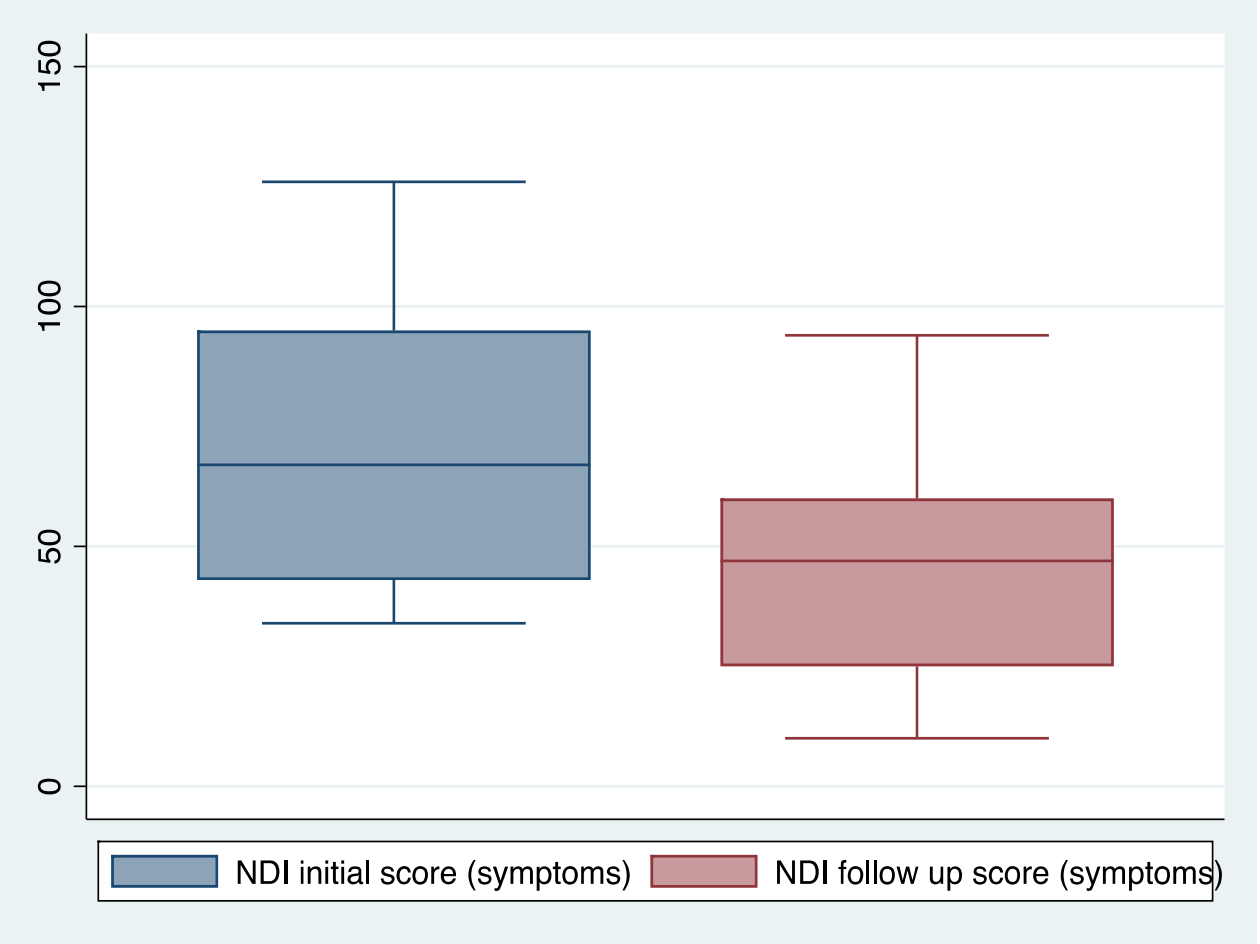
Cause or consequence of immune activation?



Each point represents a single ASV coloured by phylum and grouped on the x-axis by taxonomic genus level, size of point reflects the log counts per million (logCPM) of abundances of taxonomic ASVs

Randomized trial of wheat withdrawal followed by gluten , fructan or placebo challenge in FD

- Patients with Rome III criteria functional dyspepsia recruited from a single tertiary centre
- All were individually counselled on a diet low in both gluten and fermentable oligo- di- mono-saccharides and polyols (FODMAPs) by a clinical dietitian, which was followed for 4 weeks (elimination diet phase)
- Those who had a ≥30% response to the run-in diet, as measured by the Nepean Dyspepsia Index, were then subsequently re-challenged in RANDOM order with gluten, fructan and placebo containing bars
- Those with symptoms which significantly reduced during the elimination diet, but reliably reappeared (a mean change in overall dyspeptic symptoms of ≥30%) with gluten or fructan re-challenge were deemed to have wheat induced FD.
- 11 patients (75% female, mean age 43 years)
- Of the initial cohort, 9 patients completed the elimination diet phase of whom 4 qualified for the rechallenge phase
- The gluten free, low FODMAP diet led to an overall improvement in symptoms of functional dyspepsia in the diet elimination stage



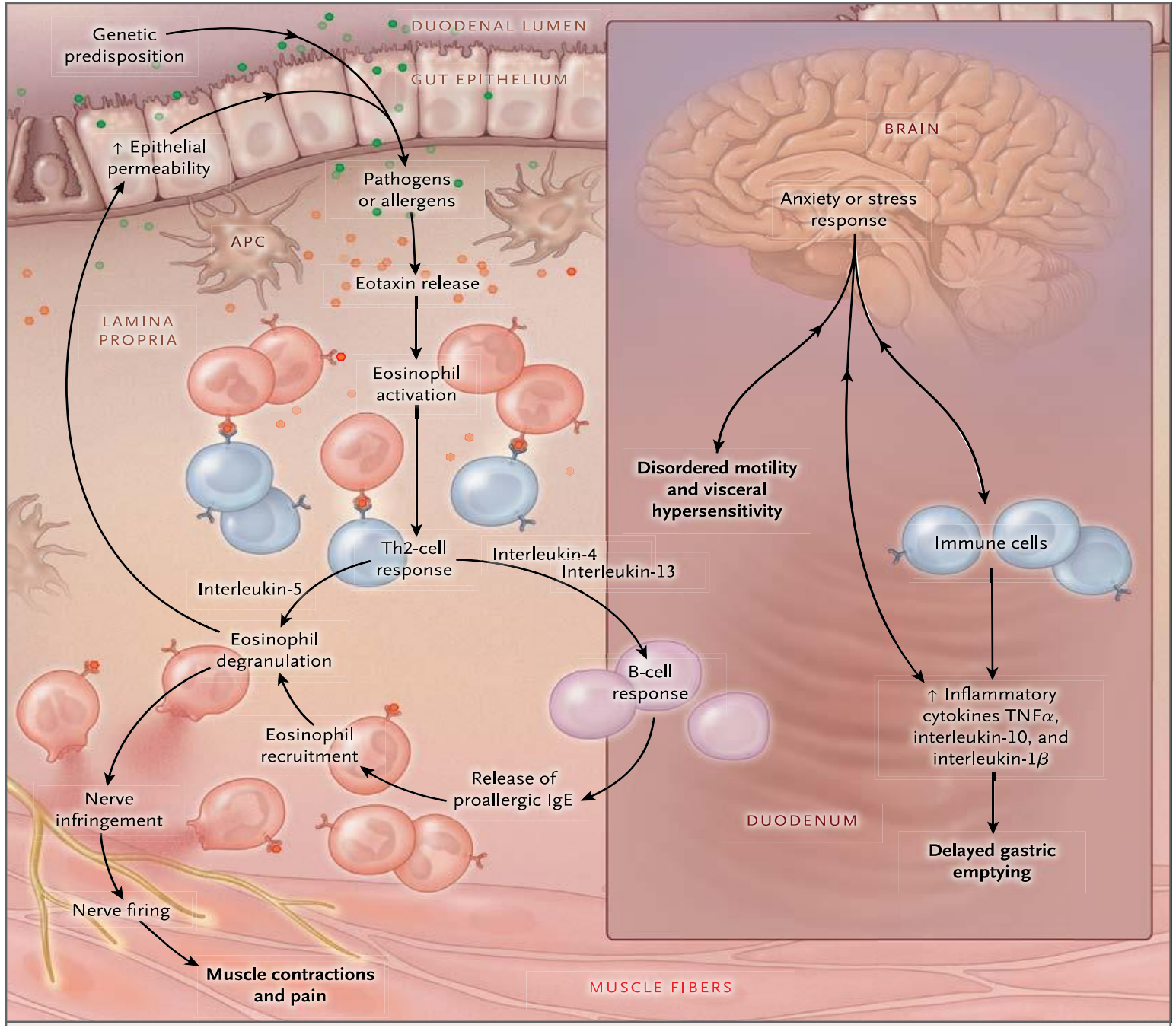
Mean symptom scores before and after gluten free, low FODMAP diet (p=0.087, Wilcoxon sign rank test)

NDI- Nepean dyspepsia index

A disease model for functional dyspepsia and NCGS

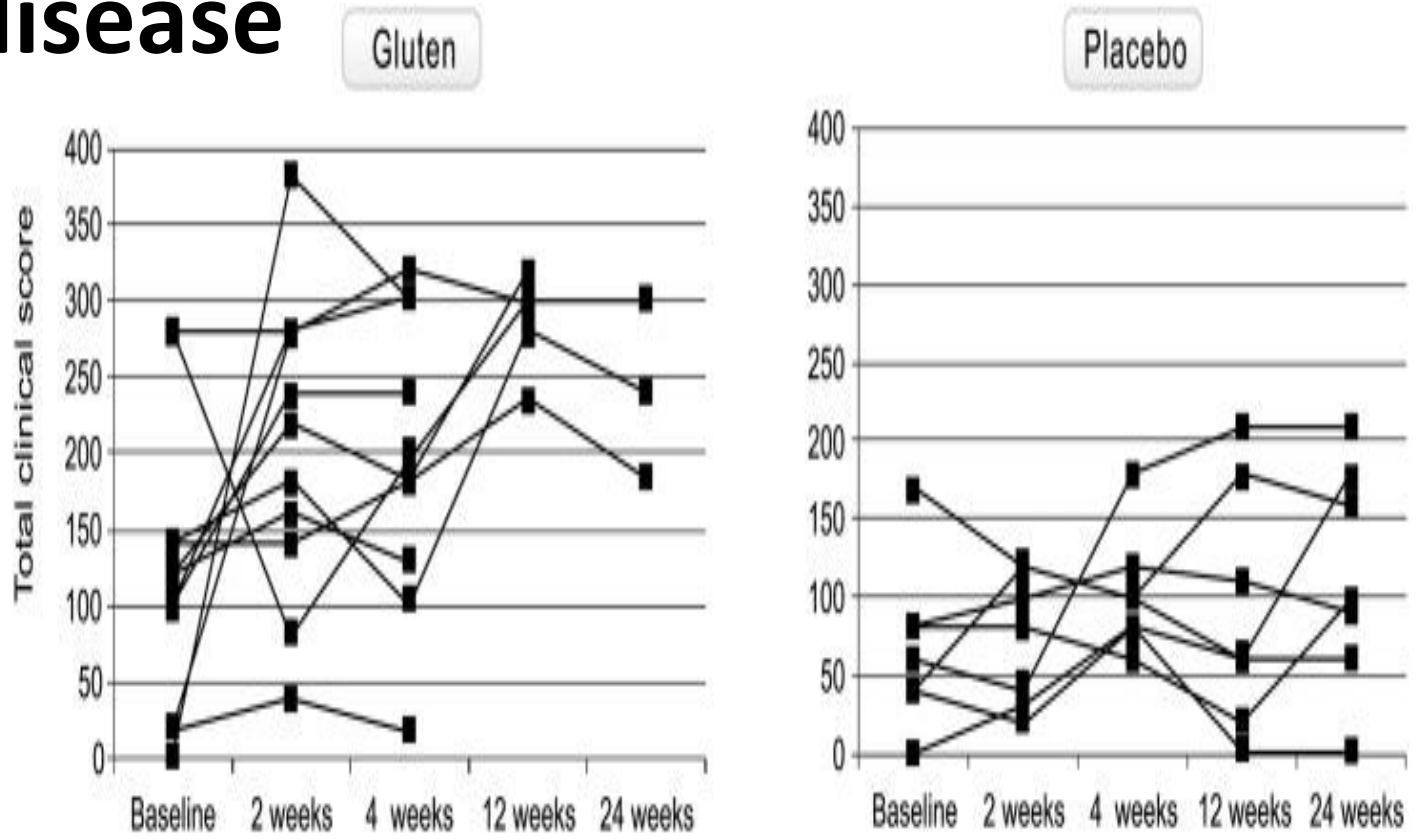
- Allergen ?gluten/ infection /microbiome change→ barrier disruption → Th2/17 type immune response → eosinophilic recruitment and degranulation → damages submucosal nervous system → altered gastroduodenal function

Talley, Ford. NEJM 2015;373(19):1853-63



NCGS vs. missed celiac disease

- Double-blind randomized clinical trial of gluten *vs.* placebo rechallenge
- >18 years of age, HLA-DQ2/8+, negative celiac serology but gluten-dependent lymphocytic enteritis (>25/100 enterocytes, no other causes), GI symptoms, clinical & histological remission
- 18 randomized: 11 gluten (20 g/day) and 7 placebo



- At baseline, 5/11 in gluten group had a celiac IEL cytometric pattern, and 2 had IgA tTG deposits: after gluten challenge, same 5 had increased CD3+γδ+ IEL
- Presence of celiac tissue markers at baseline biopsy on a gluten-free diet allowed classifying 9 out of the 18 (50%) patients as having probable 'celiac lite' disease

Rosinach et al. PLoS One 2016;11:e0157879

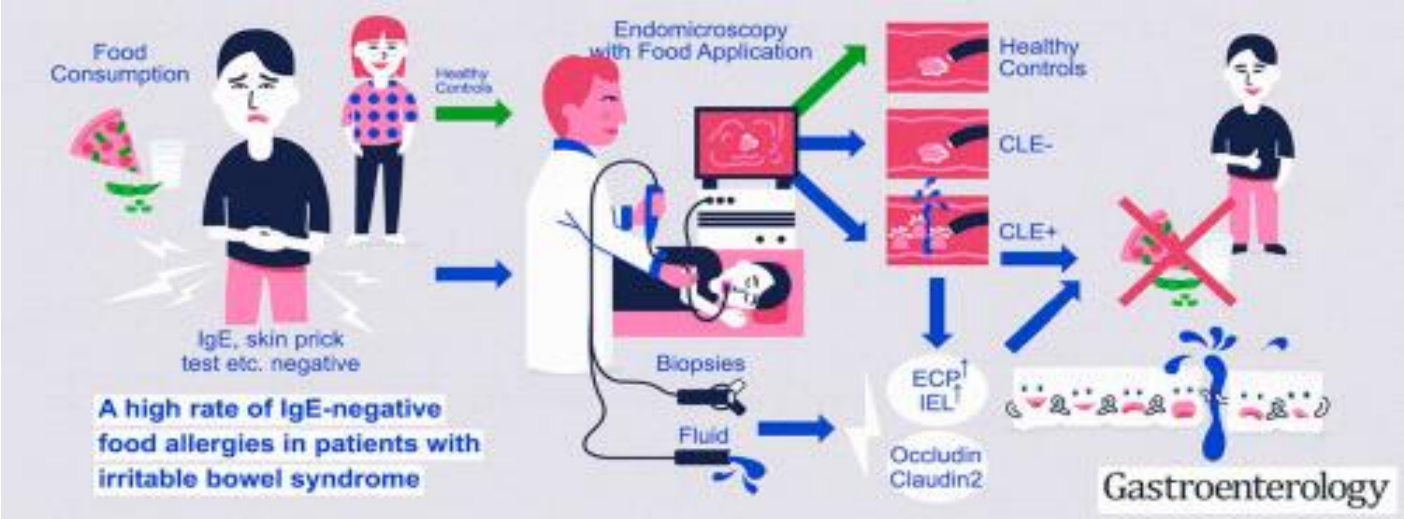
Non-celiac gluten sensitivity: a subset may have subclinical celiac disease?

YES	NO
• Lymphocytic duodenosis • Gamma delta T cells present • Mucosal anti-tTG deposits • Anti-gliadin antibodies	• HLA DQ2/8 no more common in NCGS than general population • Not associated with tTG antibodies • No enteropathy

- Likely not a homogenous group
  - Some with subclinical celiac disease, with increased IELs – “celiac lite”
  - Some with a separate true disease process (NCGS)?

Rosianch et al. PLoS One 2016;11:e0157879

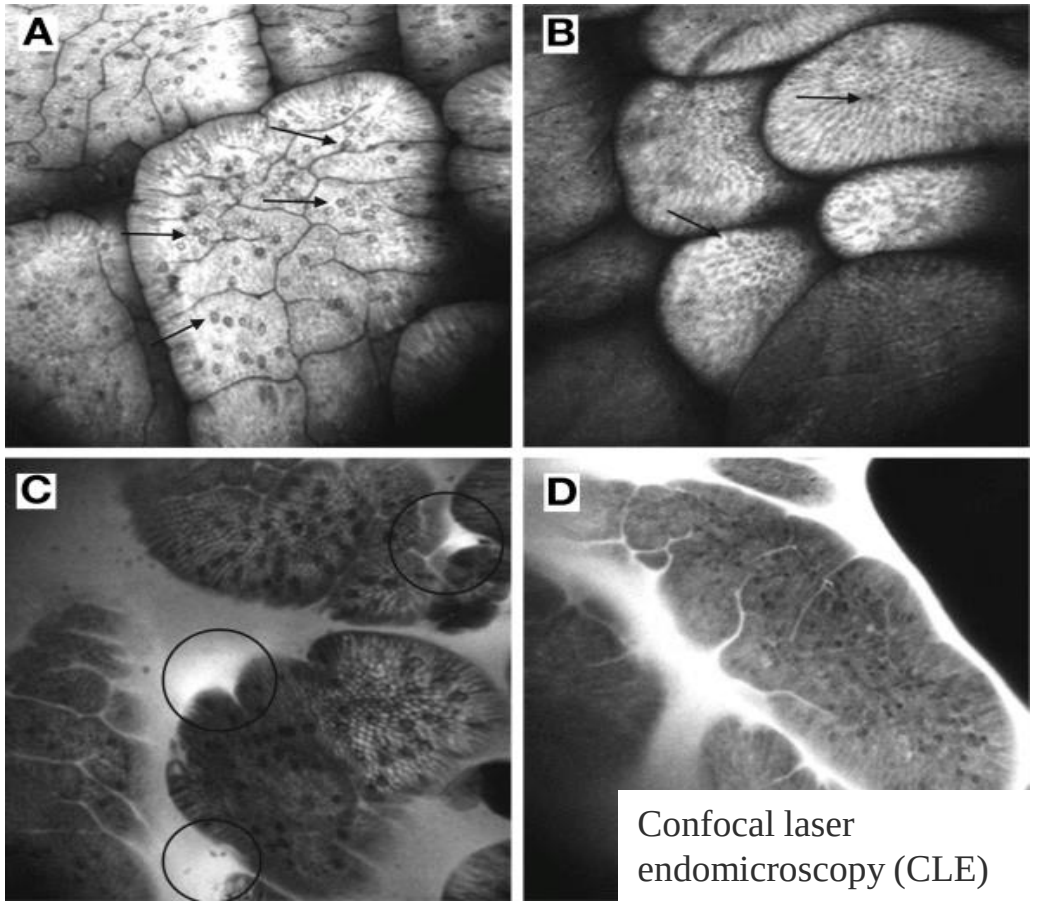
Duodenal immune activation and diet in IBS



- IBS received 4 duodenal challenges with each of 4 common food via endoscope, followed by CLE (N= 108: 76 CLE$^+$ (70%); *46 (61%) reacted to* wheat)
- IELs higher in duodenal biopsy from CLE$^+$ vs CLE$^-$ or controls
- Eosinophil degranulation increased, and levels of eosinophilic cationic protein higher in duodenal fluid from CLE$^+$ vs. controls

Fritscher-Ravens et al. Gastroenterology 2019;157(1):109-118

> 50% of IBS have nonclassical food allergy, with immediate disruption of the intestinal barrier upon exposure to antigens



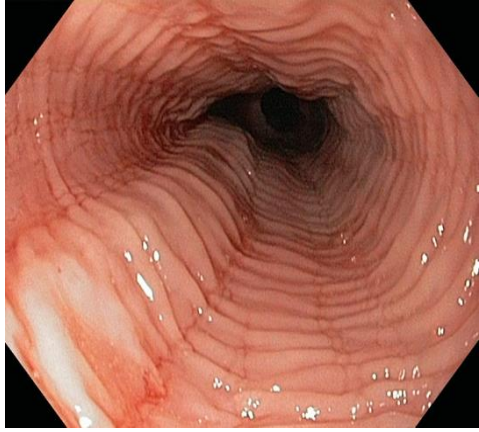
Confocal laser endomicroscopy (CLE)

(A) Baseline CLE$^+$ with multiple lymphocytes present (*arrows* IEL)
(B) low lymphocyte numbers in HC
(C) positive reaction to food antigen mucosal breaks/leaks, (*circles*)
(D) End stage of a positive reaction

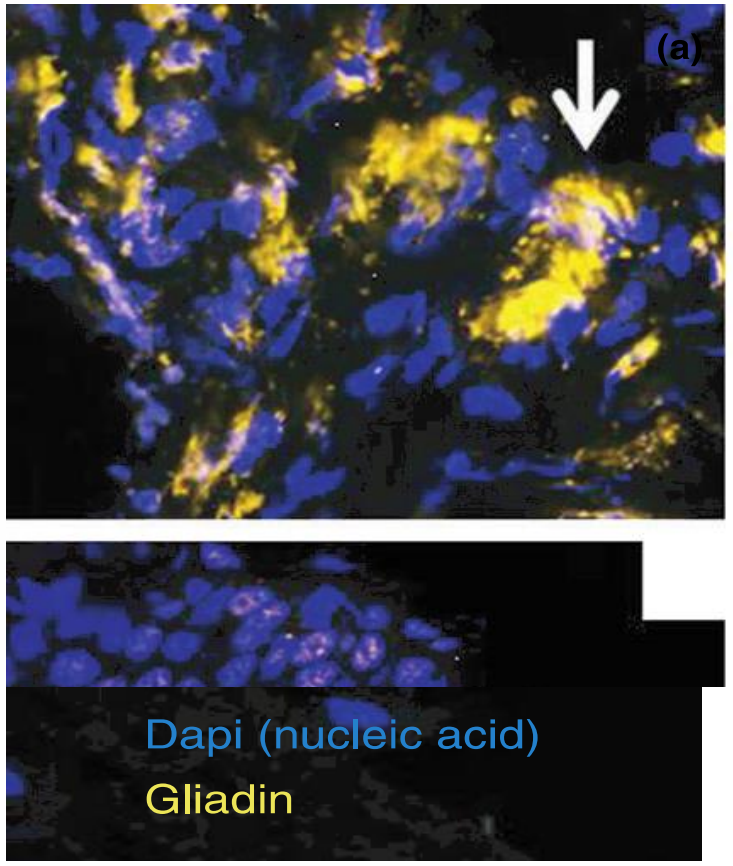
Presence of intraepithelial food antigen in patients with active eosinophilic oesophagitis

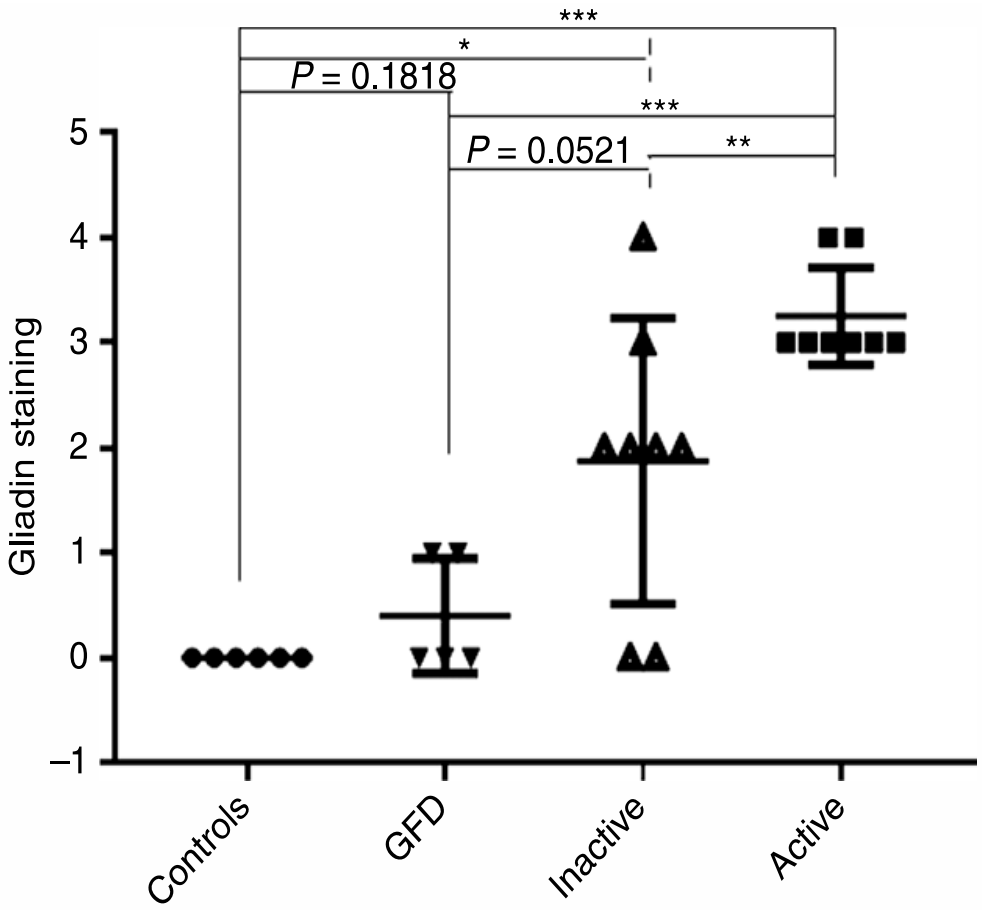
Aliment Pharmacol Ther 2017; **45**: 427–433

E. V. Marietta, D. M. Geno, T. C. Smyrk, A. Becker, J. A. Alexander, M. Camilleri, J. A. Murray & D. A. Katzka



- Anti-gliadin antibody staining in the oesophagus in EoE patients but not controls
- Suggests gliadin potential antigen driving eosinophilia
- No further staining if esophagus perfused with soy sauce (undigested gluten)
- Partially digested gluten may be key (role of microbiome?)

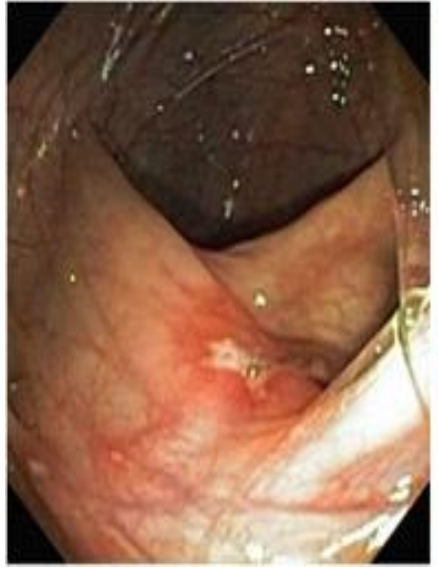


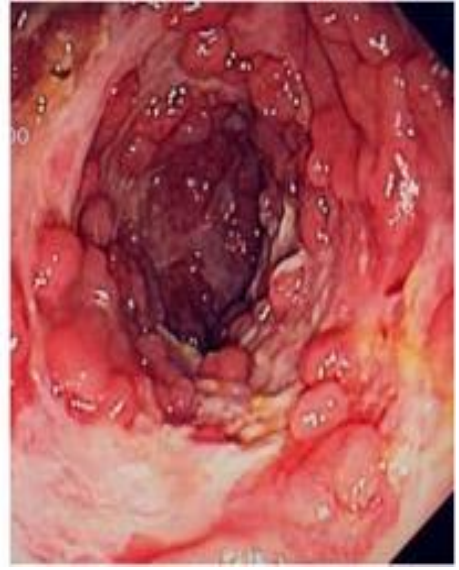


A Study Evaluating the Bidirectional Relationship Between Inflammatory Bowel Disease and Self-reported Non-celiac Gluten Sensitivity

Inflamm Bowel Dis • Volume 21, Number 4, April 2015

Imran Aziz, MBChB, MRCP, Federica Branchi, MD,*,† Katherine Pearson,* Josephine Priest,* and David S. Sanders, MD, FRCP, FACG**





- IBD n=145, IBS and dyspeptic controls
- 27% of IBD patients self report wheat sensitivity
- Crohn's patients with SRWS also more likely to have severe or stricturing disease

TABLE 3. Characteristics of Crohn's Disease Patients with and Without SR-NCGS

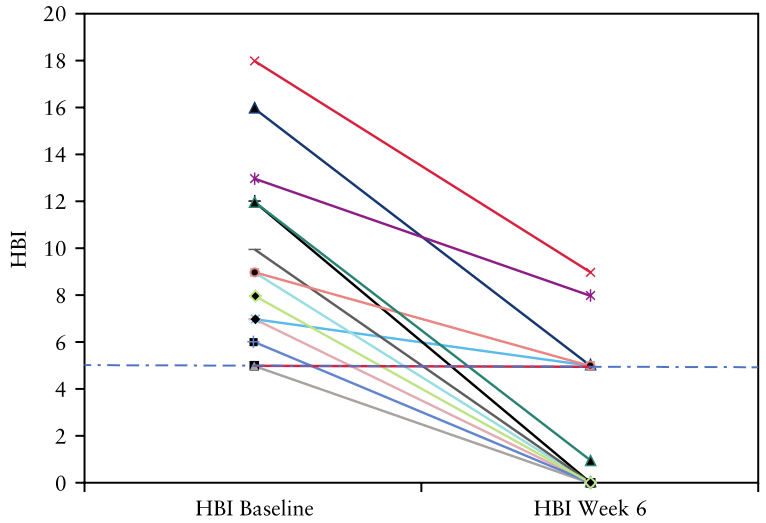
	Crohn's Disease with SR-NCGS (n = 22)	Crohn's Disease Without SR-NCGS (n = 53)	*P*
Crohn's disease severity			
Penetrating disease, %	0 (0)	4 (7.5)	0.19
Stricturing disease, %	9 (40.9)	10 (18.9)	0.046
Mean CDAI score (SD)	228.1 (128)	133.3 (104.7)	0.002

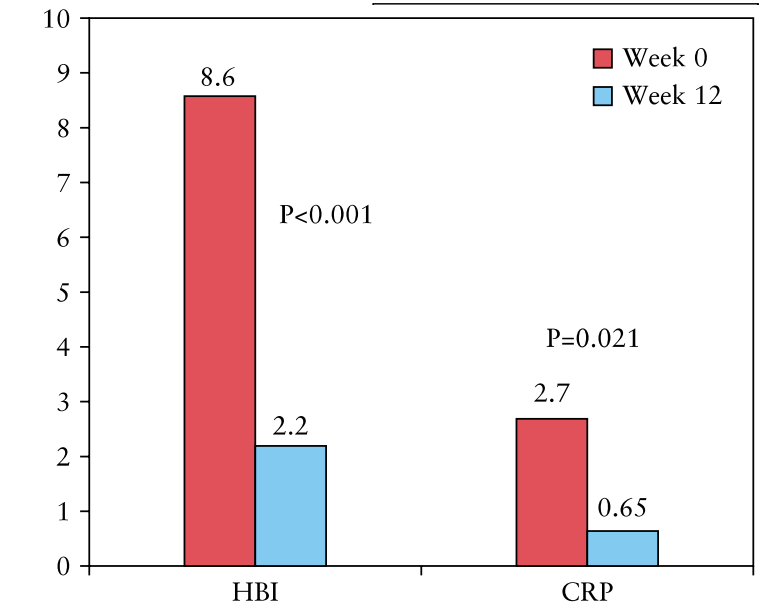
Dietary Therapy With the Crohn's Disease Exclusion Diet is a Successful Strategy for Induction of Remission in Children and Adults Failing Biological Therapy

Rotem Sigall Boneh, Chen Sarbagili Shabat, Henit Yanai, Irit Chermesh, Sivan Ben Avraham, Mona Boaz, Arie Levine

Journal of Crohn's and Colitis, 2017, 1205–1212

- 21 Crohn's patients; 48% failed biologic therapy
- Partial elemental diet; partial exclusion diet (**WHEAT** excluded)
- Clinical remission in 62% (not mucosal healing)
- Significant improvement in symptom scores and CRP



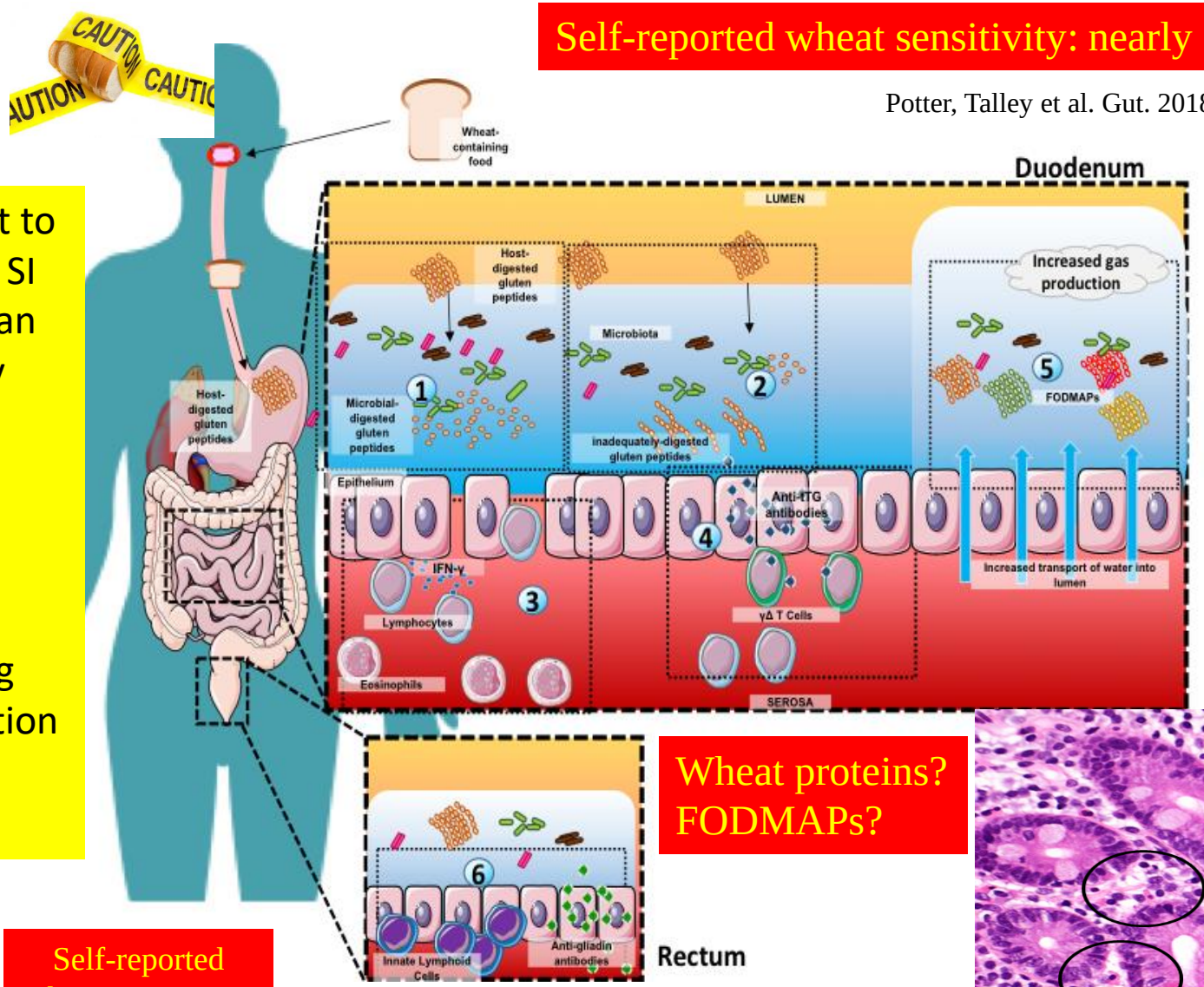


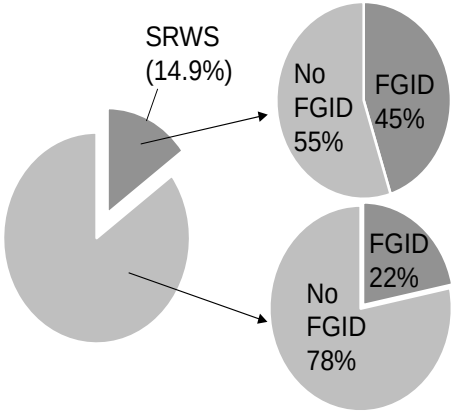
Non-celiac gluten sensitivity (NCGS): an emerging new disease?

Self-reported wheat sensitivity: nearly 50% have IBS or FD

Potter, Talley et al. Gut. 2018 doi: 10.1136/gutjnl-2018-316360

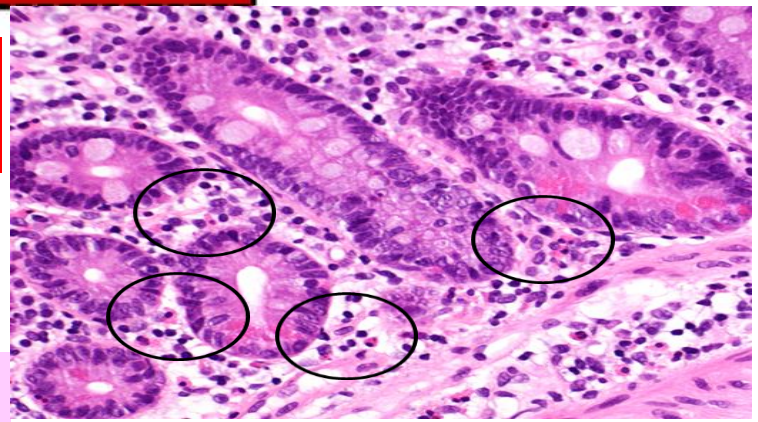
Gluten resistant to degradation by SI enzymes, but can be degraded by enzymes of bacterial and fungal origin leading to immunogenic peptides driving immune activation if permeability impaired…





Potter, Talley et al.
Am J Gastroenterol
2018;113:1036-44

Wheat proteins?
FODMAPs?



Carroccio *et al* Am J Gastroenterol 2012; 107:1898–1906
Carroccio et al. Clin Gastroenterol Hep 2018 in press

Self-reported wheat sensitivity: up to 15% population

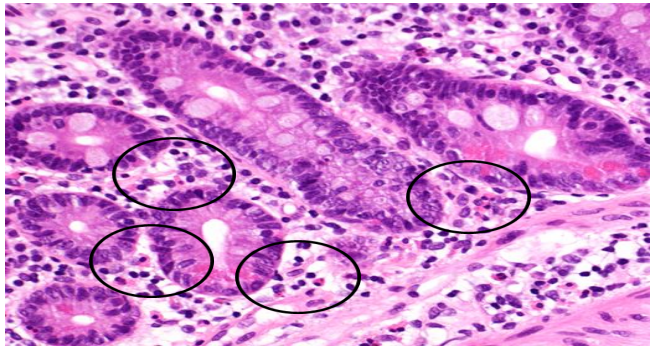
Duodenal eosinophilia (circled) in NCWS
Increased rectal eosinophils also observed
Diagnosis by double-blind wheat challenge

Case continued…

- 25 year old woman with 10 year history of daily bloating, abdominal pain after eating, loose stools and pain relief on defecation, early satiety, heartburn, lethargy, joint pain, headaches & anxiety, not responding to a gluten free diet
- tTG negative (IgA normal), previous EGD normal & normal duodenal biopsy (all testing on a gluten free diet), HLA-DQ2 positive
- Differential diagnosis includes:
  A. Celiac disease – retest on a gluten containing diet after 2 weeks
  B. Celiac "lite" – careful review of biopsy, strict GFD trial if present
  C. Non-celiac gluten sensitivity – not a disease, not a diagnosis
  D. IBS and functional (non-ulcer) dyspepsia – check Rome criteria for FGID
  E. Wheat allergy – IgE testing, consider double-blind challenge
  F. Psychiatric disorder – rule out depression etc.

- If not celiac disease or wheat allergy, management options include:
  - Trial of a low FODMAP diet, stop strict GFD, reintroduce FODMAPs slowly
  - Treat IBS and/or functional dyspepsia if low FODMAP fails– reassurance, explanation, reduce stress, targeted pharmacotherapy
  - Anti-eosinophil therapy a potential approach in those with this biomarker?

Take Home Points



- Non-celiac gluten sensitivity (NCGS) is a heterogeneous syndrome reported by 1 in 6 people – rule out celiac disease (1%) and wheat allergy (rare)
- Both intestinal and extra-intestinal symptoms described by those self-reporting wheat sensitivity, but this is not confined to NCGS
- About 50% with self-reported NCGS fulfil Rome criteria for a functional GI disorder (functional or non-ulcer dyspepsia, IBS)
- Double-blind wheat challenge testing in those self-reporting NCGS a “gold standard”
  - identifies less than 1 in 5 with probable wheat sensitivity
  - improvement on wheat exclusion may indicate fructan (FODMAP) intolerance
  - 2 in 5 respond to placebo – non-gluten physiological reaction, somatoform illness?
- A subset with NCGS have duodenal pathology (e.g. subtle eosinophilia) and immune activation, as do a subset with functional dyspepsia
- Increased IELs, no other cause identified, wheat sensitive – consider “celiac lite”
- A gluten free diet is probably <u>not</u> a healthier diet if <u>not</u> celiac: monitor!

Thank you!

Australian Gastrointestinal Research Alliance

- Professor Marjorie Walker
- Professor Mike Jones
- A/ Professor Simon Keely
- Professor Gerald Holtmann
- Professor Mark Morrison
- Dr. Michael Potter
- Dr Natasha Koloski
- Gillian Harris
- Bernadette Rickards
- Raquel Cameron