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BLOATING, FUNCTIONAL BOWEL DISEASE AND FOOD SENSITIVITY: NON-CELIAC GLUTEN SENSITIVITY, THE LOW-FODMAP DIET AND BEYOND?




Ingestion of food and IBS

- Can trigger or aggravate IBS symptoms; for example, ~60% within 15 minutes in 28%, up to 3 hours in 93% of IBS patients

Simrén et al, Digestion 2001

- Diet is 1^o behavioural factor manipulated by women with IBS


Jamieson et al, Clin Nurse Spec 2007

- Multiple potential mechanisms via (for example):
 - stimulating mechanoreceptors and chemoreceptors
 - inciting inflammation and/or damage
 - altering gut microbiota
- 



Dietary strategies in IBS

Changed from patient-initiated and whole food, patient-focussed strategies → attention to *specific components*

- ▣ Fermentable carbohydrates → low FODMAP diet
 - ▣ Proteins → gluten-free diet
 - ▣ Bioactive food chemicals → low chemical diet
 - ▣ Lipids → avoidance of fatty foods as adjuncts
- 

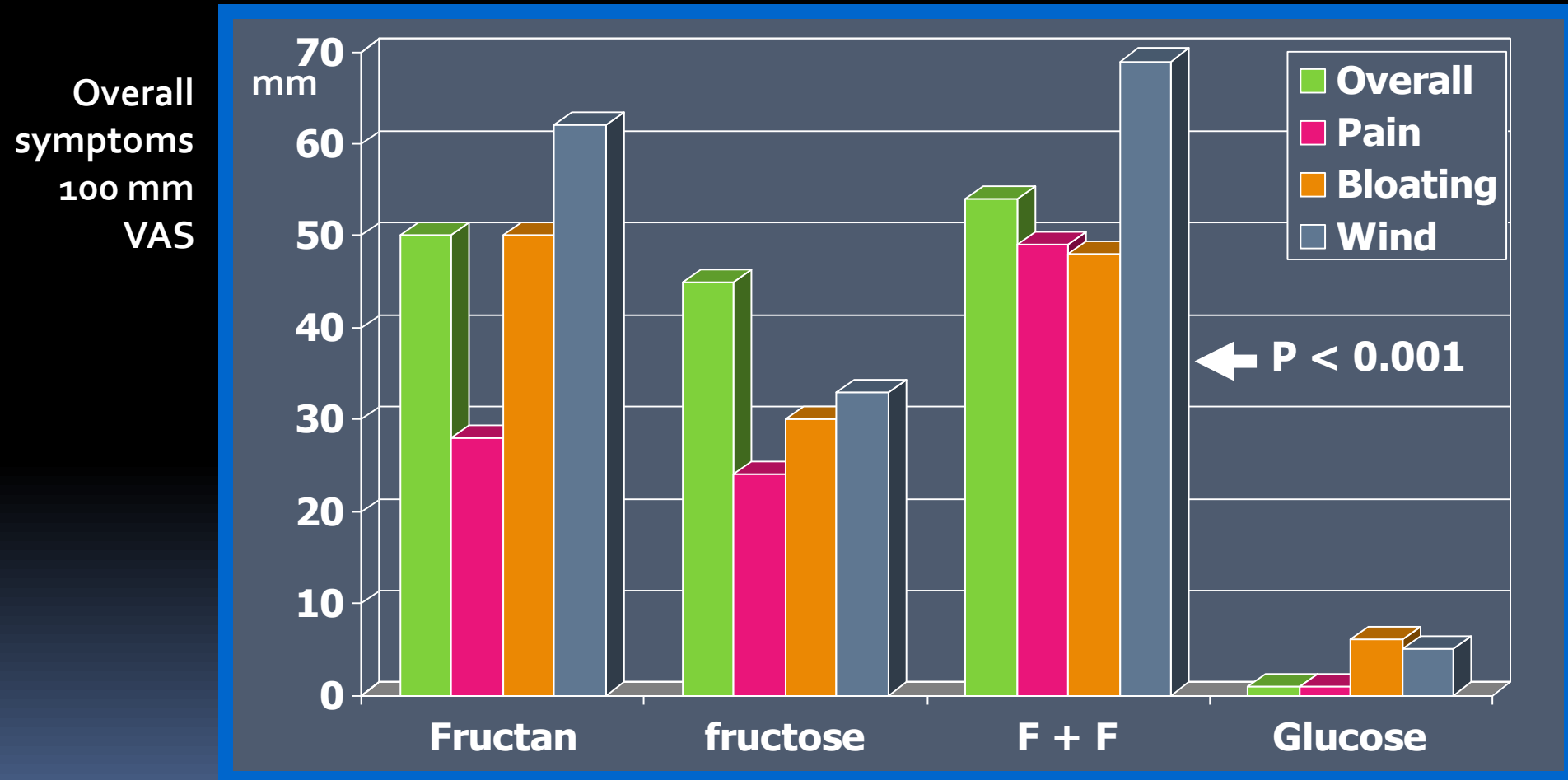
Short-chain carbohydrate malabsorption

- Well known to mimic IBS symptoms
- 'Lactose intolerance'
 - Lactose-free diet not effective in IBS
- 'Fructose intolerance' ± sorbitol
 - 'fructose-free diet' efficacious in uncontrolled reports
- Galacto-oligosaccharides
 - Avoidance of 'windy' foods
- Fructose and fructan restriction
 - Effective in observational study of patients with IBS and fructose malabsorption (breath H₂ test)

Shepherd & Gibson JADA 2006

Randomised placebo-controlled rechallenge cross-over study in patients with IBS + fructose malabsorption (n=25)

→ *fructans and fructose were pathogenically involved & additive*



Hypothesis:

Consider all indigestible and slowly-absorbed short-chain carbohydrates collectively

Fructose



Lactose



Fructans



GOS



Polyols



*Similar & additive physiological effects → distend intestine
via osmotic effect + gas production*

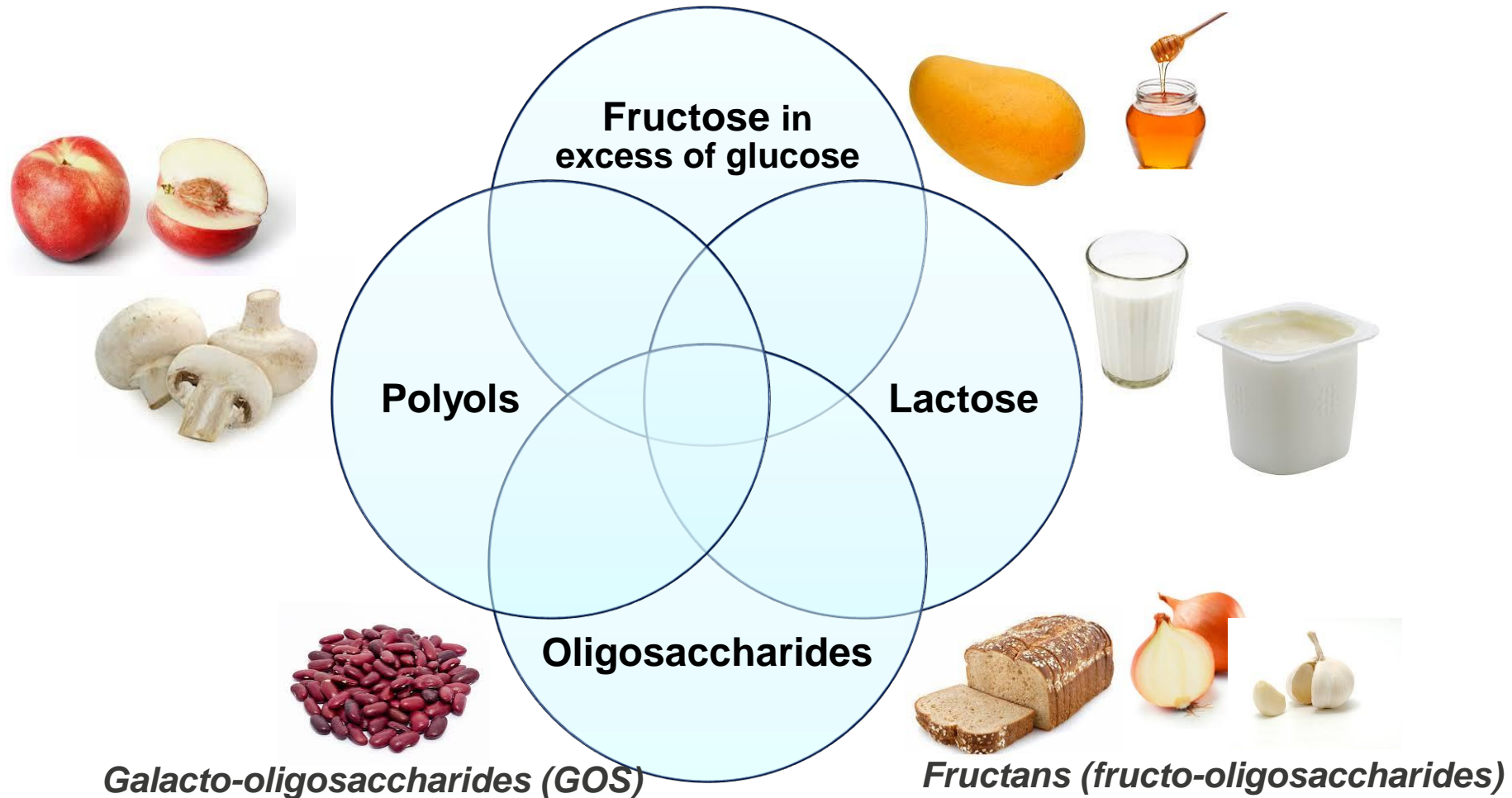


Symptoms

FODMAP concept was born!

FODMAPs

Fermentable **O**ligo- **D**i- & **M**ono-saccharides **A**nd **P**olyols



FODMAPs: *absorption patterns*

- POORLY ABSORBED IN ALL

- **Oligosaccharides**: fructo- (FOS) & galacto- (GOS)
 - No small intestinal hydrolases

Osmotic +
Fermentation +++

- SLOWLY ABSORBED IN ALL

- **Free fructose** (i.e., fructose in excess of glucose)
- **Polyols**: sorbitol, mannitol
- Proportion passively absorbed (~30%)

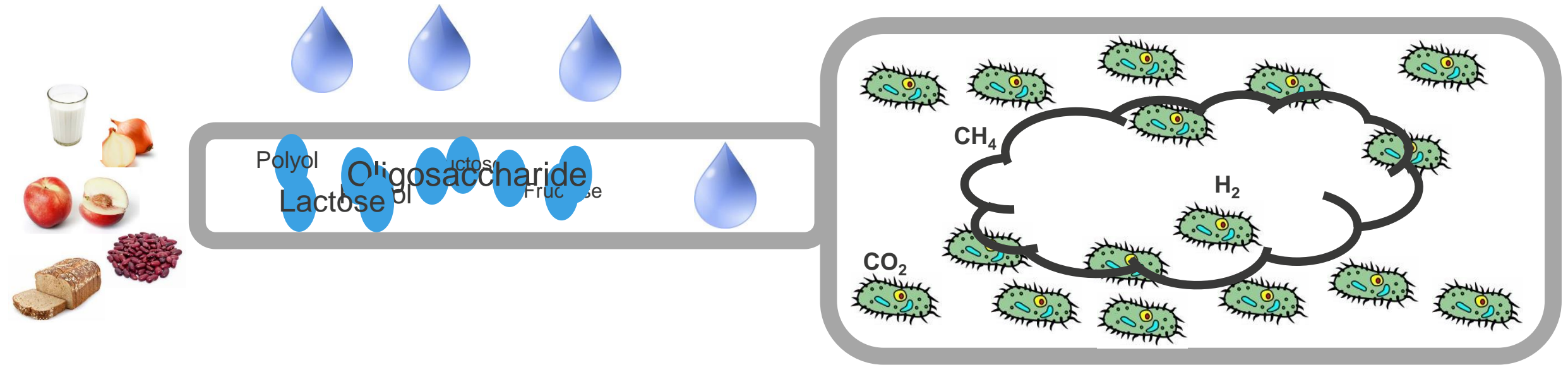
Osmotic +++
Fermentation +

- POORLY ABSORBED IN ONLY SOME

- **Lactose** 10-95% depending upon ethnicity, other factors
→ Recognise lactose malabsorption via breath H₂ testing

Osmotic +++
Fermentation ++

Major mechanisms of action of FODMAPs



↑ water delivery

↑ gas production



Luminal distension



Visceral hypersensitivity

Diarrhoea and/or constipation,
pain, bloating, wind

Barrett et al APT 2010

Ong et al JGH 2010

Marciani et al GE 2010

Murray et al AJG 2014

**FODMAP-induced
luminal distension**

```
graph TD; A[FODMAP-induced luminal distension] -- "Visceral hypersensitivity" --> B["Abdominal pain<br/>Bloating<br/>Distension<br/>Diarrhoea /or<br/>constipation"]; A -- "Normal visceral sensation" --> C[No symptoms];
```

**Visceral
hypersensitivity**

**Abdominal pain
Bloating
Distension
Diarrhoea /or
constipation**

**Normal visceral
sensation**

No symptoms

Low FODMAP diet: 'TOP-DOWN' approach

Avoid all foods high in FODMAPs ('unsafe')
Replace with foods low in FODMAPs ('safe') in
each food group

Efficacy

4-6 weeks

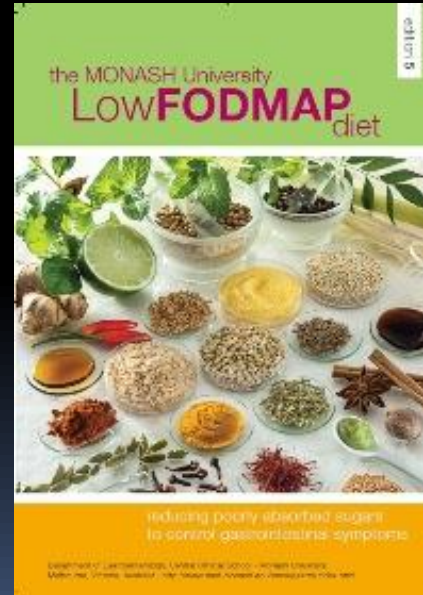
No benefit
& adherent

STEP DOWN
according to
tolerance



Key to the low FODMAP diet

- Must know what foods should be avoided and what are 'safe'
- Ongoing program of measurement of food content using a combination of HPLC & enzymatic assays (including international foods)



Muir et al JAFRC 2008, 2009
Biesiekierski et al JHND 2011
Yao et al JHND 2013

<http://www.med.monash.edu/cecs/gastro/fodmap/>

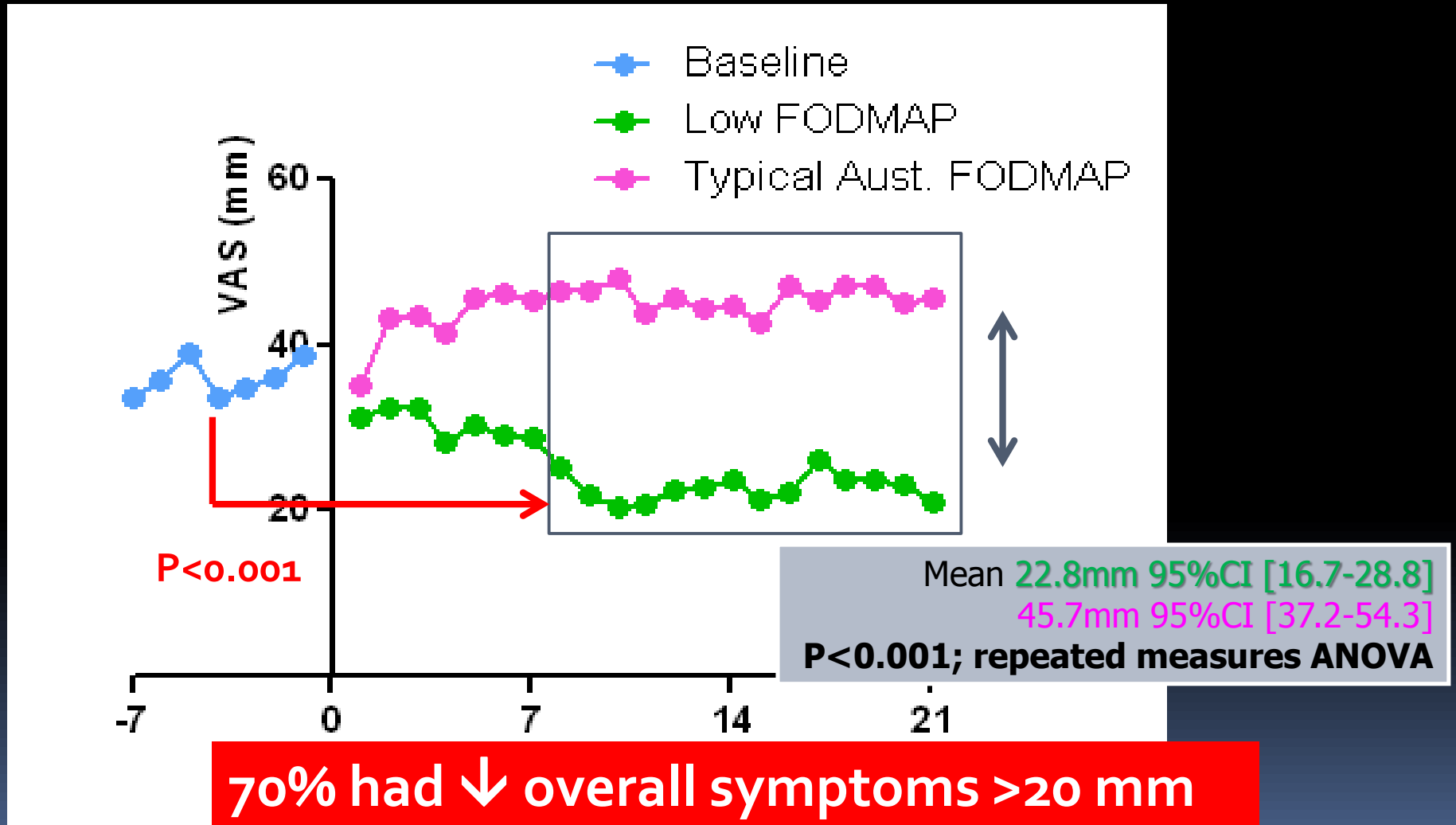
Evidence-base for efficacy of low FODMAP diet

- Challenge with individual FODMAPs
- Observational cohort studies (retro- & prospective)
- RCT cross-over – rechallenge
- RCT cross-over – *all food supplied*
 - high vs low FODMAP diets
 - typical Aussie intake vs low FODMAP
- RCTs cross-over – *dietitian-taught*
- RCTs low FODMAP vs habitual diet
- Non-randomised comparative study

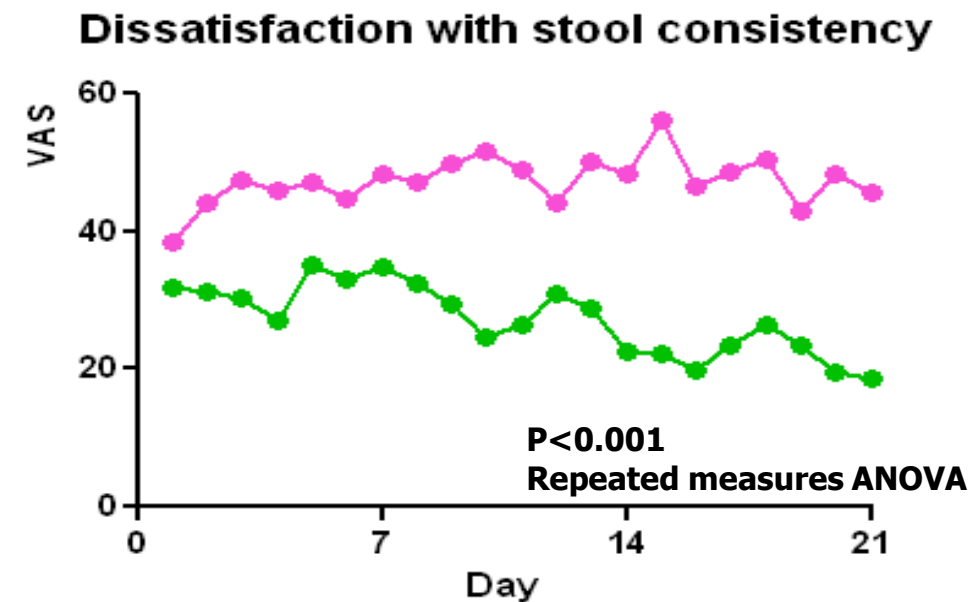
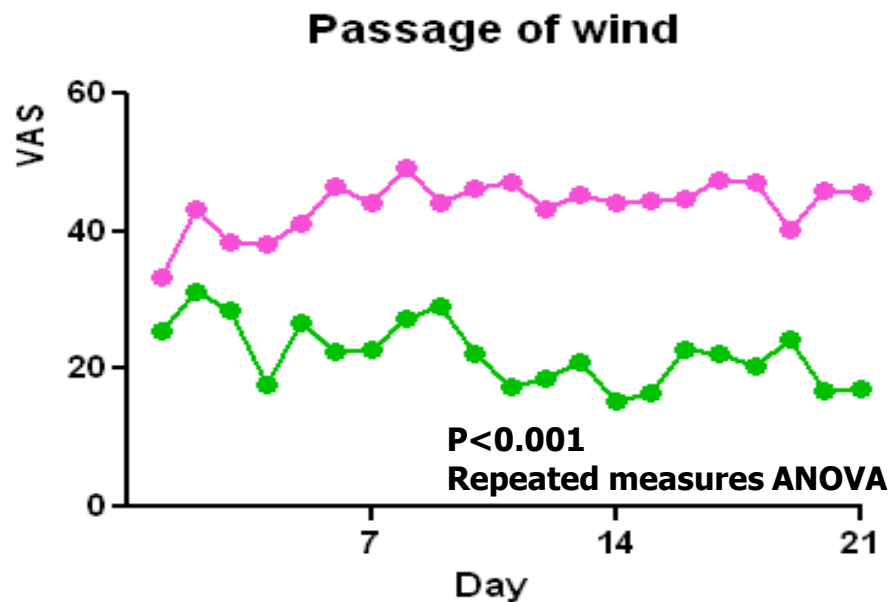
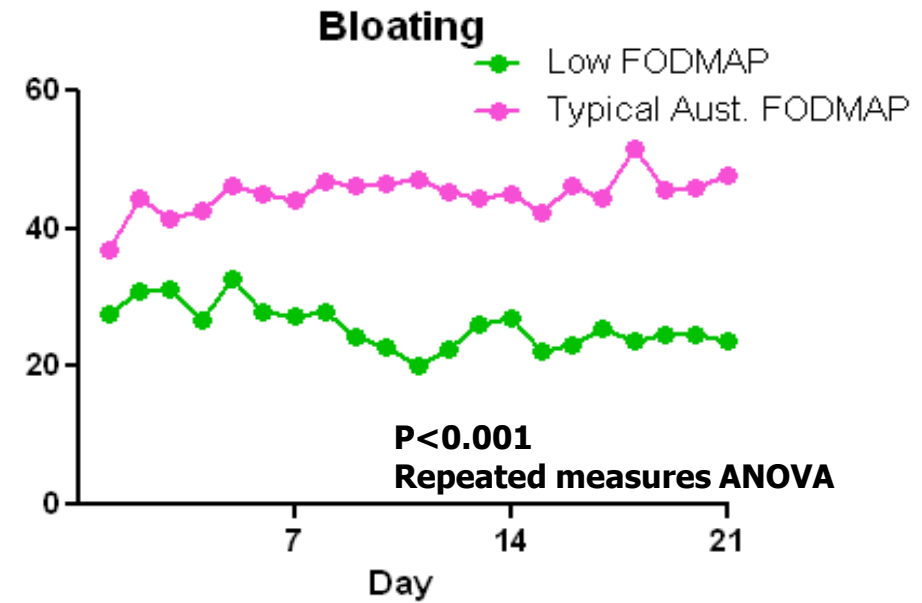
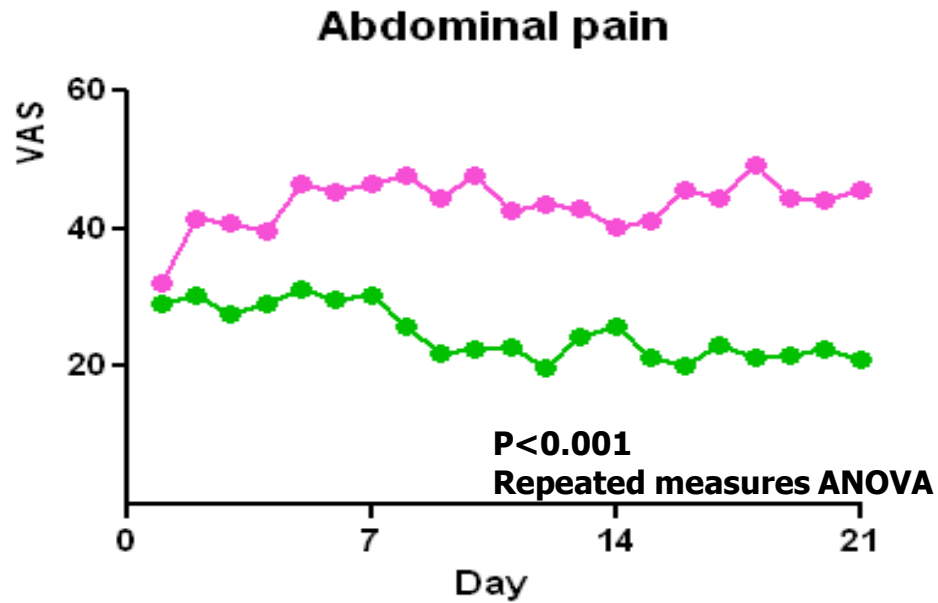
Australia
UK
NZ
Denmark
USA
Canada
Hong Kong
Ireland
Spain
et al

Efficacy in 50-83% of patients – usually ~70%

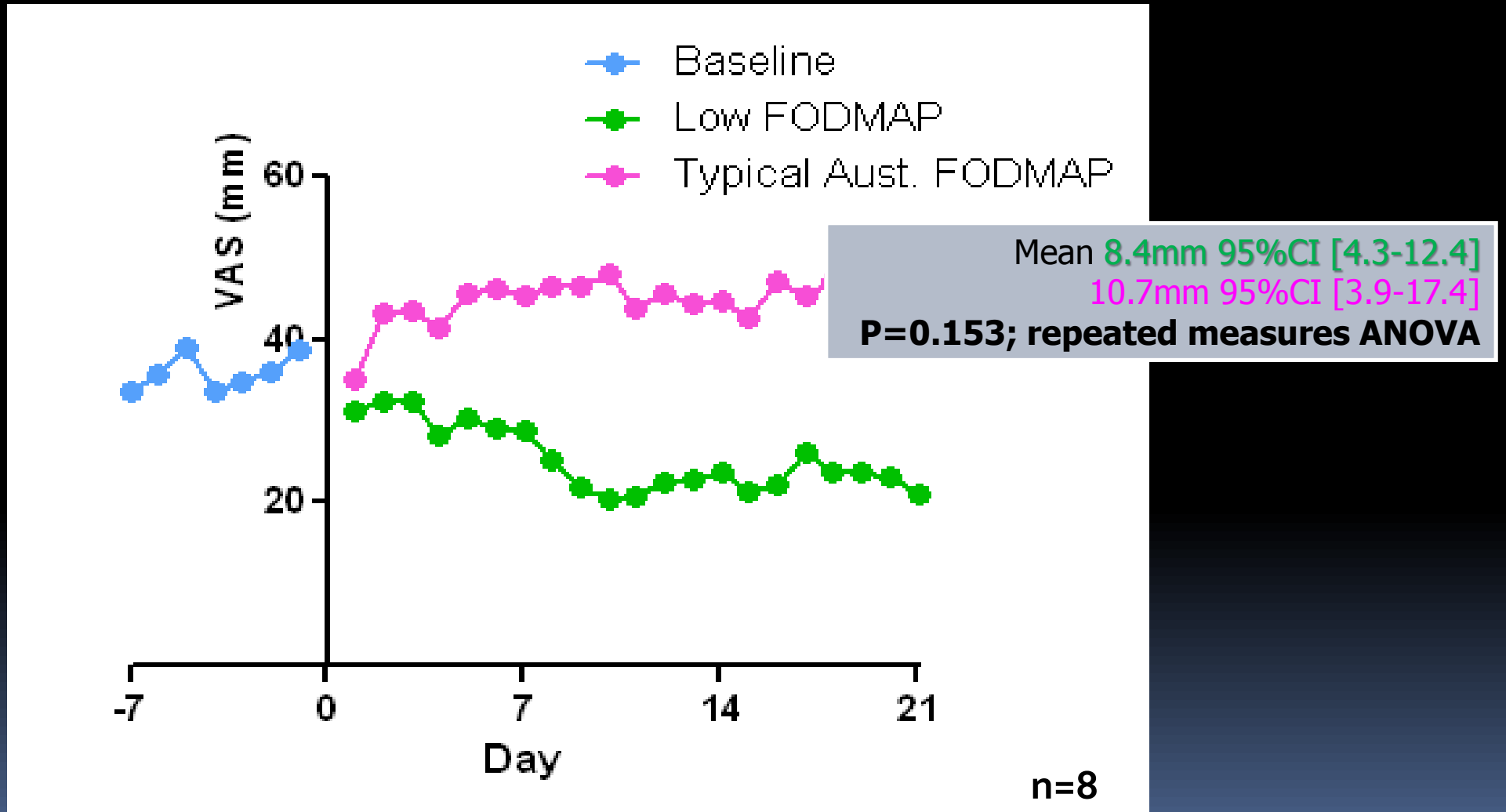
Effect of altering dietary FODMAP content on overall abdo symptoms in IBS (n=30) *all food provided*



Effect on specific symptoms in IBS (n=30)



Changing FODMAP intake does not affect abdominal symptoms in healthy controls





Meta-analysis

Marsh et al Eur J Nutr 2015

RCTs $n=6$

- ↓IBS SSS: (OR=0.44 [0.25-0.76])
- ↑IBS-QOL: OR=1.84 [1.12-3.03]
- ↓symptom severity for
 - abdominal pain: OR=1.81 [1.13-2.88]
 - bloating: OR=1.75 [1.07-2.87]
 - overall symptoms : OR=1.81 [1.11-2.95]

Non-randomised interventions $n=16$

- ↓IBS SSS: OR=0.03 [0.01-0.2]
- ↑IBS-QOL : OR=3.18 [1.60-6.31]
- ↓symptom severity for
 - abdominal pain
 - bloating
 - overall symptoms

Efficacy of low FODMAP diet is durable

- 24 patients with IBS
- Prospectively observed over 6 months
- Dietitian-taught diet – 2 visits only
- 91% had reintroduced FODMAPs

VAS compared to baseline	6 weeks	6 months
% improving >20 mm	72%	74%
Overall improvement (mm) Mean [95% CI]	30 [19, 42]	30 [16, 43]

How easy is the low FODMAP diet to follow?

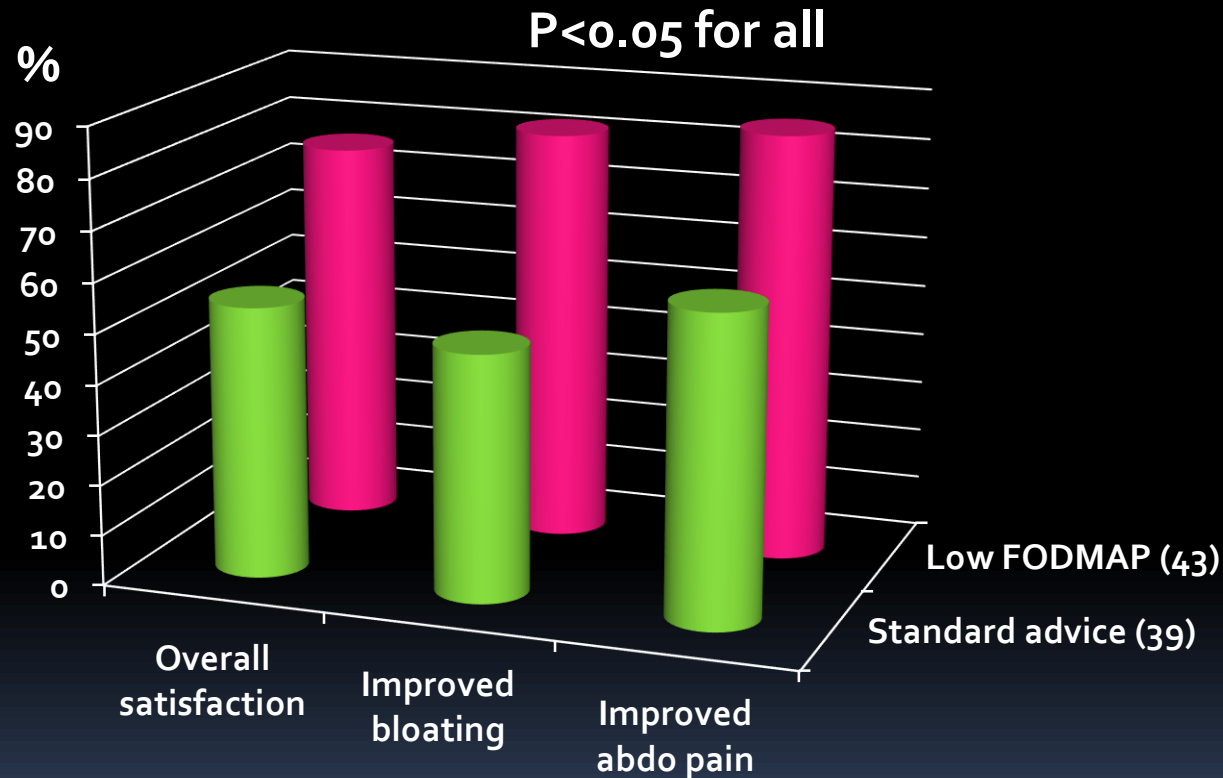
Not difficult to learn but needs patient buy-in

- ▣ NZ prospective study (n=90)
 - ➔ 61% found diet easy to follow
 - ➔ 41% easy to incorporate into their life

deRoest et al, Int J Clin Pract 2013

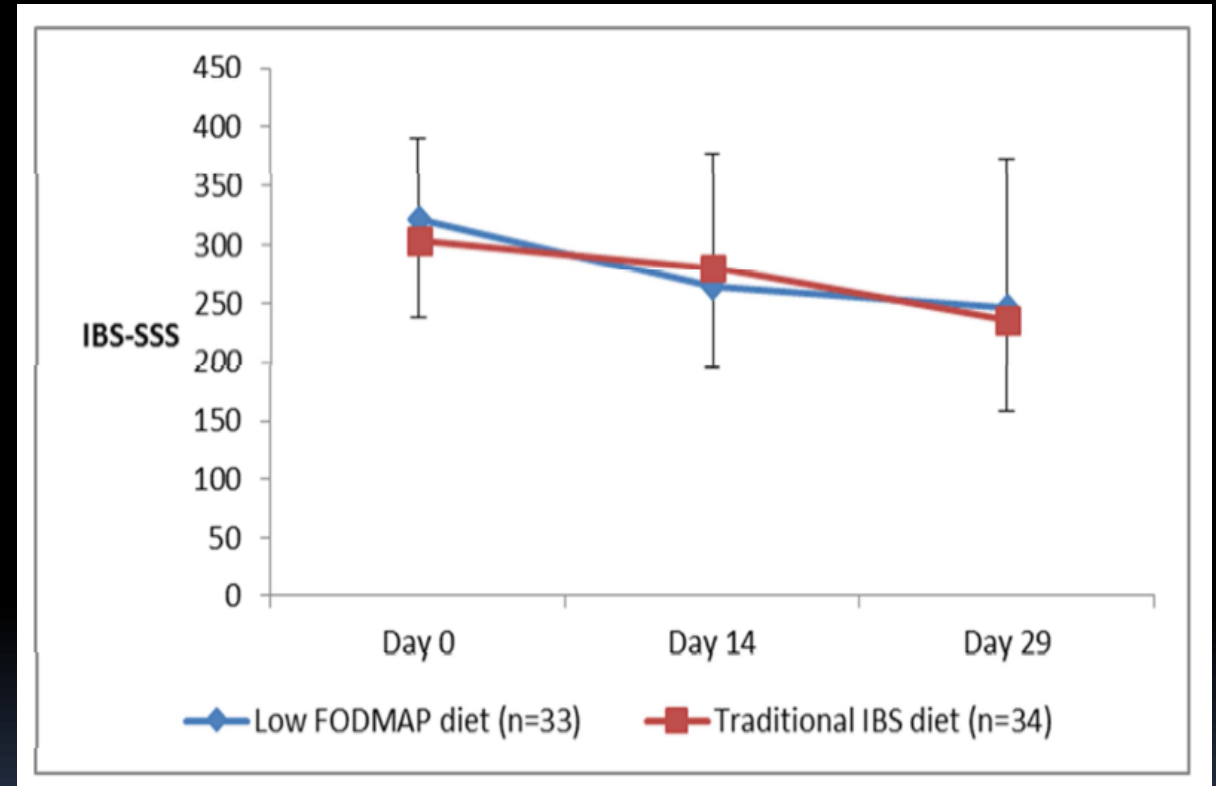
Comparison of low FODMAP with standard NICE diet

Non-randomised; UK



Staudacher et al, J Hum Nutr Diet 2011

Randomised; Sweden



50%
response

46%
response


Bohn et al, Gastroenterology 2015

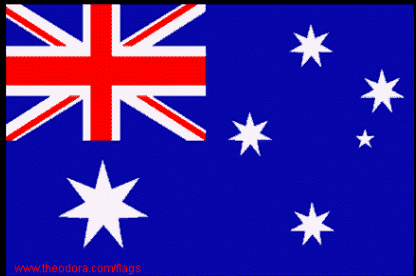
Potential interpretations

- Low FODMAP diet not delivered well ??
 - Only study with response rate <60-75%
 - Small true FODMAP difference achieved (mainly lactose reduction)
- No advantage in delivering an initial strict low FODMAP diet ??
 - Most patients can successfully partly re-introduce foods to tolerance
 - So why start strictly ??
→ *Needs evaluation*



Gluten-free or wheat-free diets in IBS

- Are they efficacious?
 - Are symptoms due to gluten or other component of wheat?
- 



Wheat/gluten avoidance

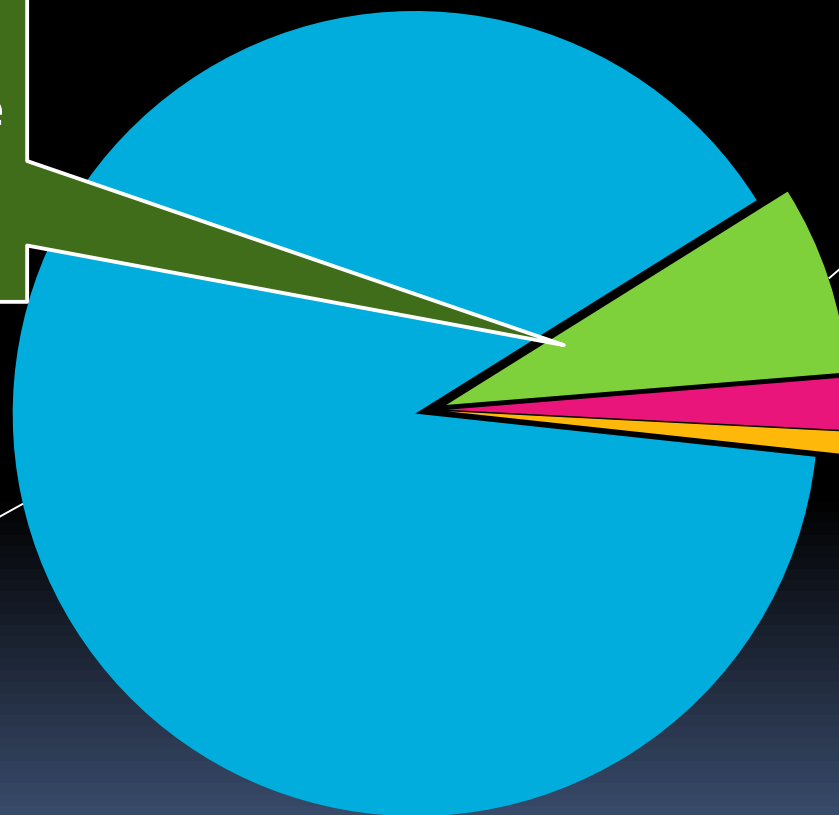
CSIRO Food & Health Survey

Dec 2010-Feb 2011; n = 1184 ≥ 18 years old

Most likely to be

- Women who like the alternative
- but are not neurotic, illogical or hypochondriacal

Non wheat
avoiders
89%



Symptoms
8%

85% bloating or
abdominal pain
32% fatigue

No
symptoms
2%

Coeliac
disease
<1%

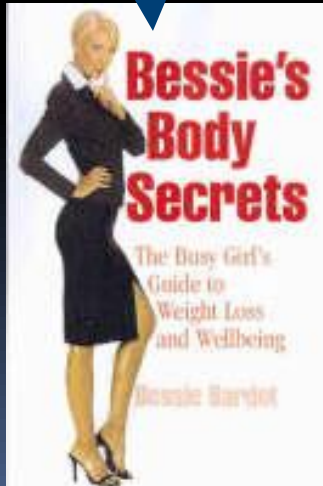
Strong advocates for gluten-free for all

Celebrities

Pseudoscientists

et al

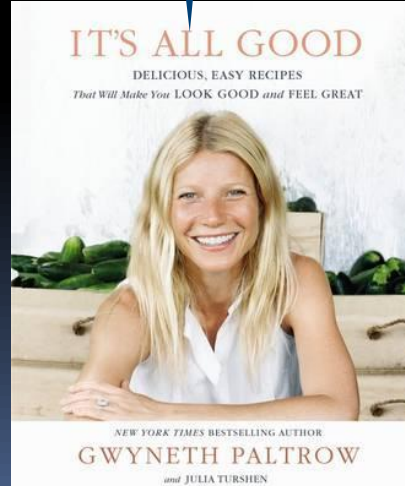
Beautiful
body



Many
illnesses



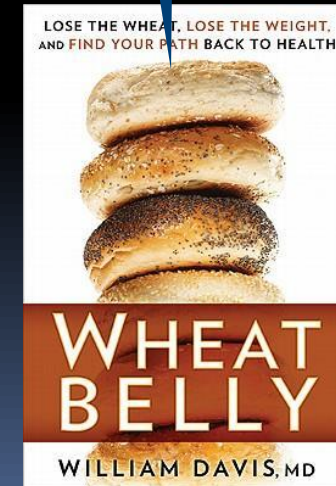
Look and
feel good



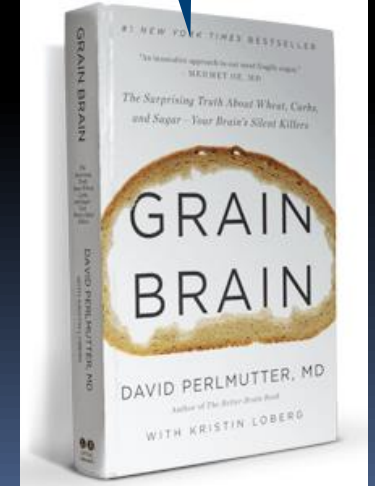
How to
go from
#2 to #1



Weight
loss



Brain fog



Non-coeliac gluten sensitivity

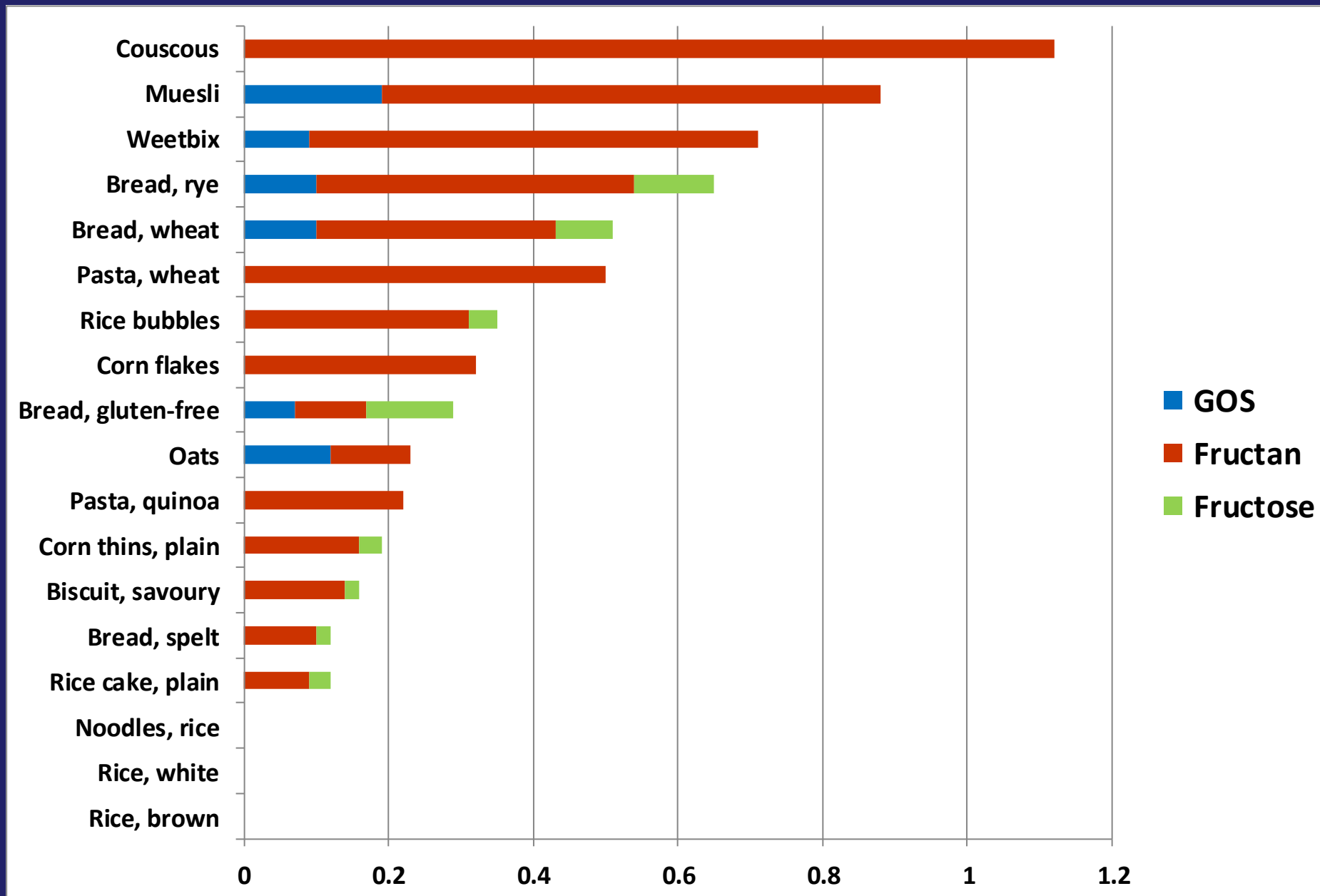
Expert consensus

- Gut symptoms
- Extraintestinal symptoms
 - malaise, fatigue, headache, numbness, mental confusion ('brain fog'), anxiety, sleep abnormalities, fibromyalgia-like symptoms, skin rash
 - gastro-oesophageal reflux disease, aphthous stomatitis, anaemia, depression, asthma, rhinitis

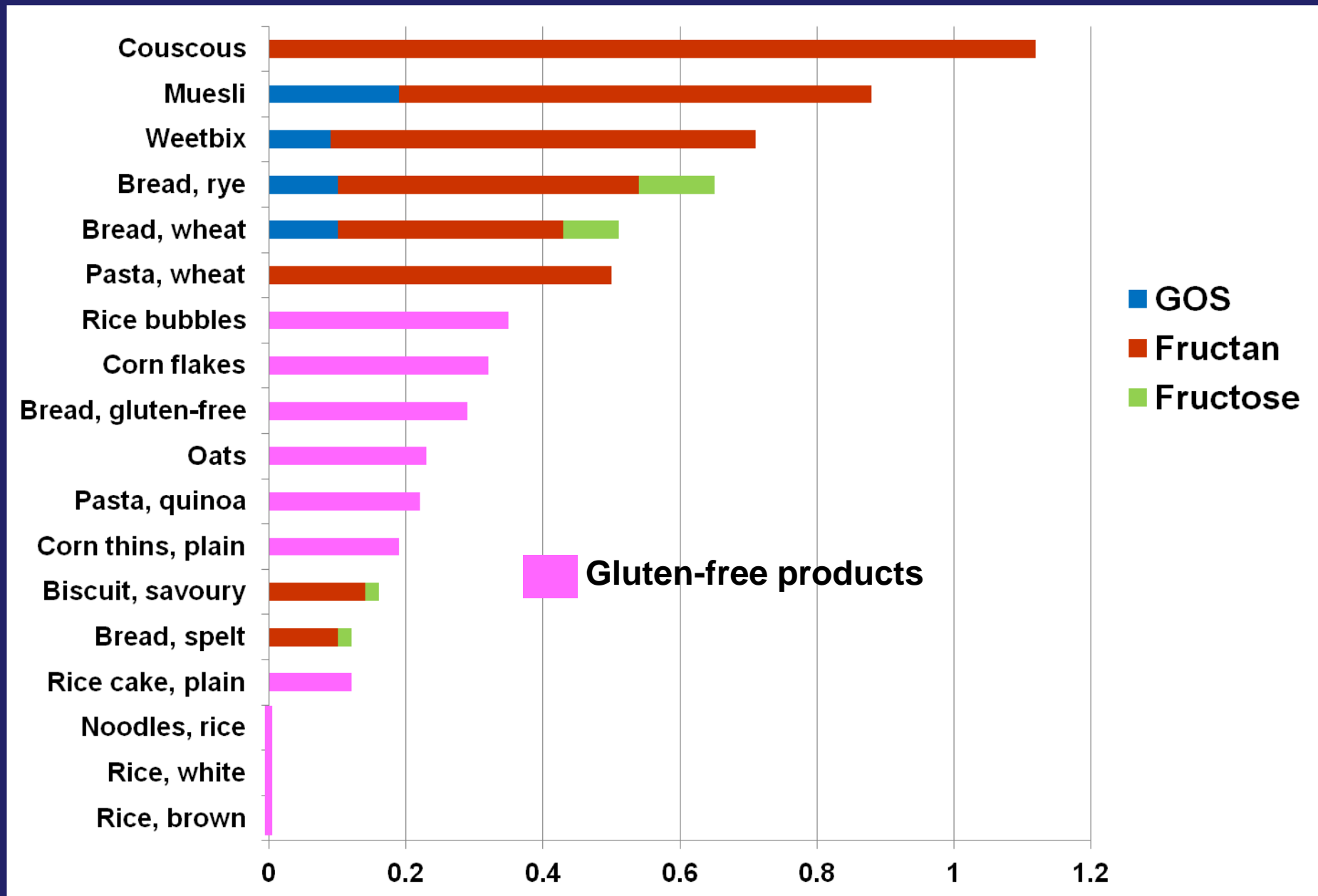
Catassi et al. Non-celiac gluten sensitivity: the new frontier of gluten related disorders.

Nutrients 2013

FODMAP content of cereal products per serve



FODMAP content of cereal products per serve





Wheat intolerance?

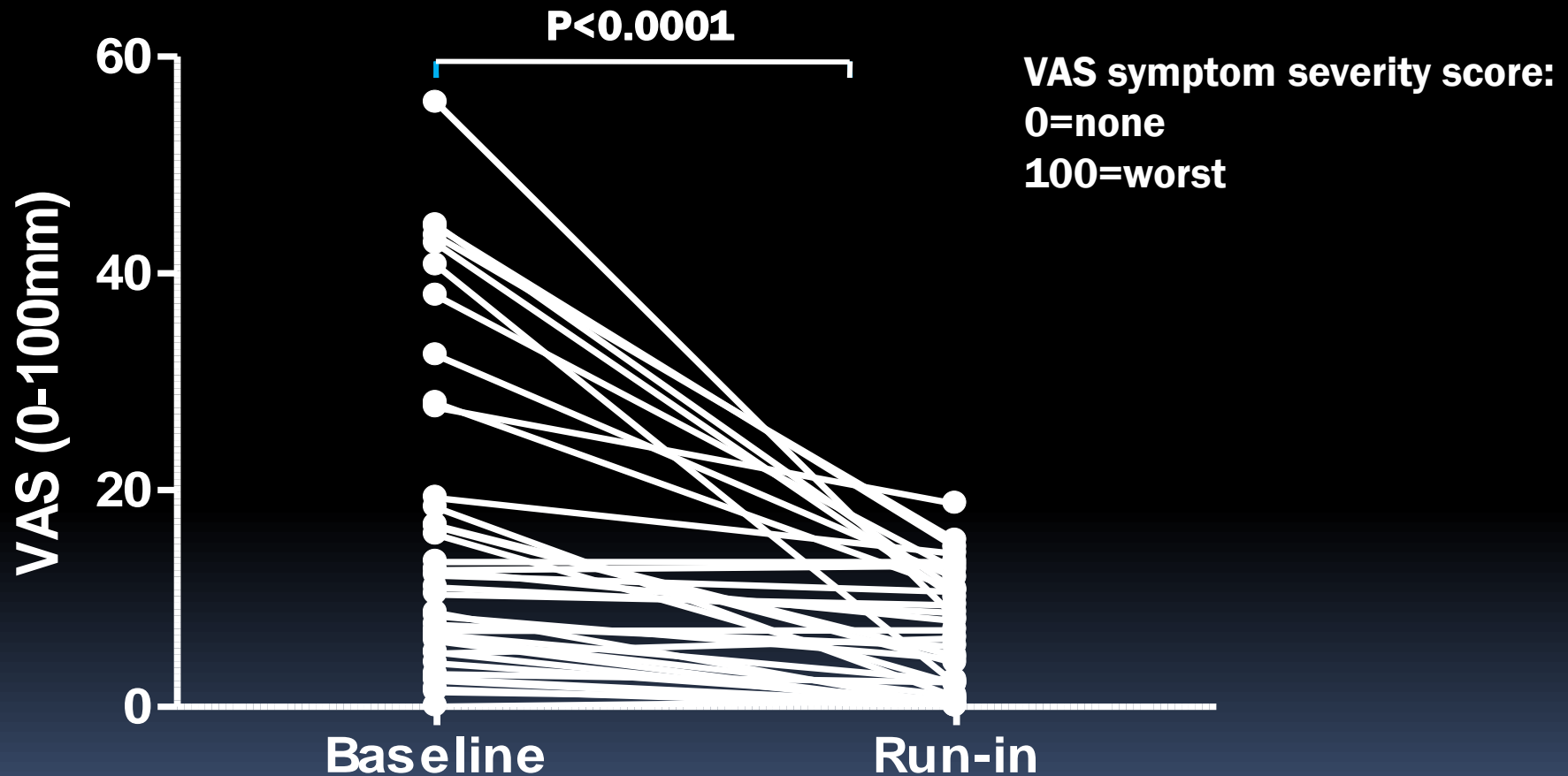
FODMAPs

vs

wheat protein (gluten)



Effect of ↓ FODMAPs on overall symptoms on 36 patients with self-reported NCGS



Wheat protein (gluten) sensitivity?

Gold standard investigation

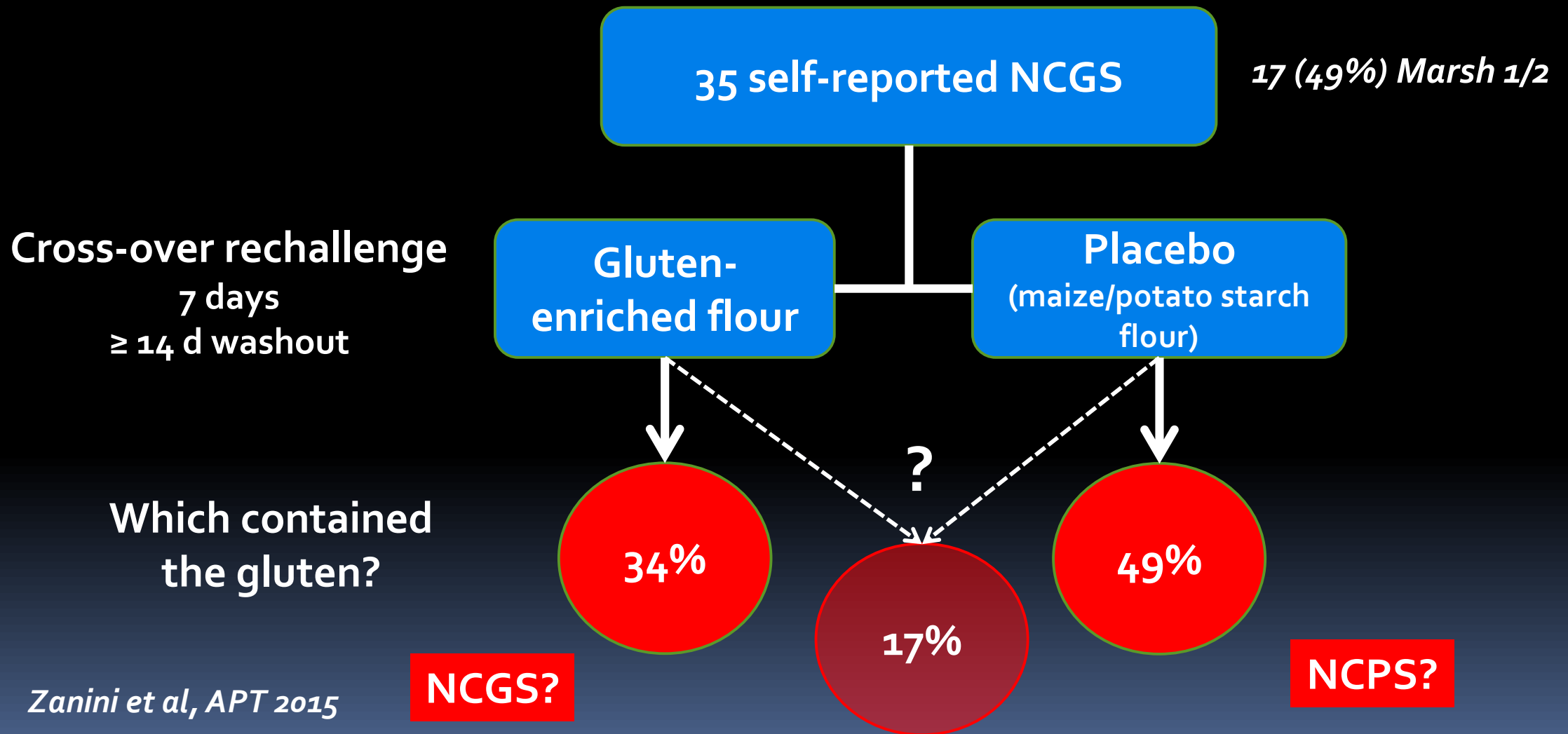
Improvement on elimination → double-blind, placebo-controlled (DBPC) cross-over challenge

4 published randomised controlled trials (n=231)

For wheat protein ('NCGS')

- **Challenge with minimal FODMAP content (bread is not suitable!)**
- **Nocebo effect → blinding + placebo essential**

#3 Italian study: Cross-over

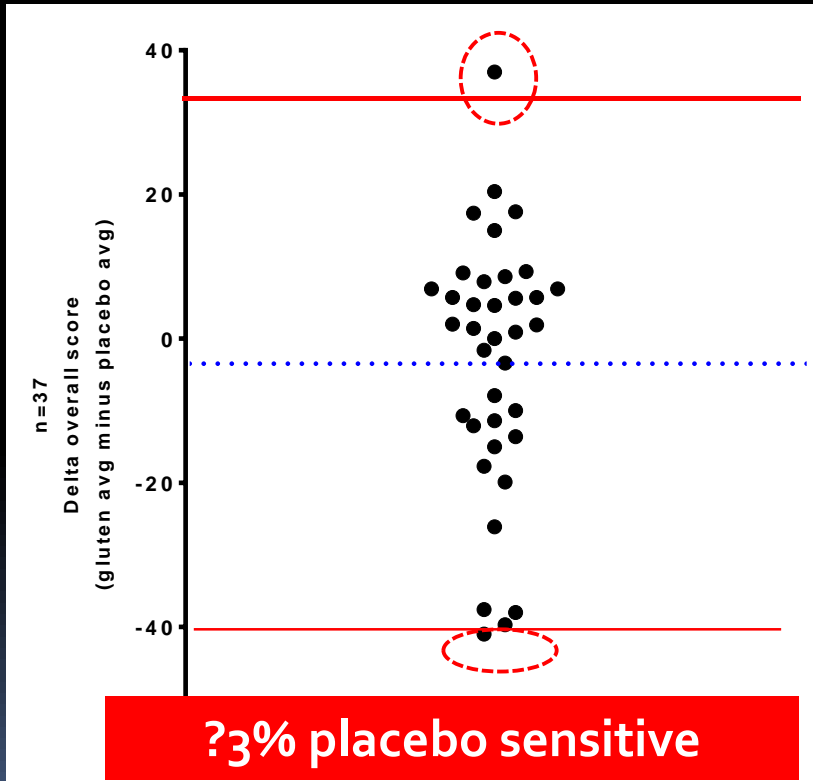


Assessing individual responses:

Difference between gluten & placebo effects in RCT re-challenges

? 3% gluten sensitive

Overall GI symptoms

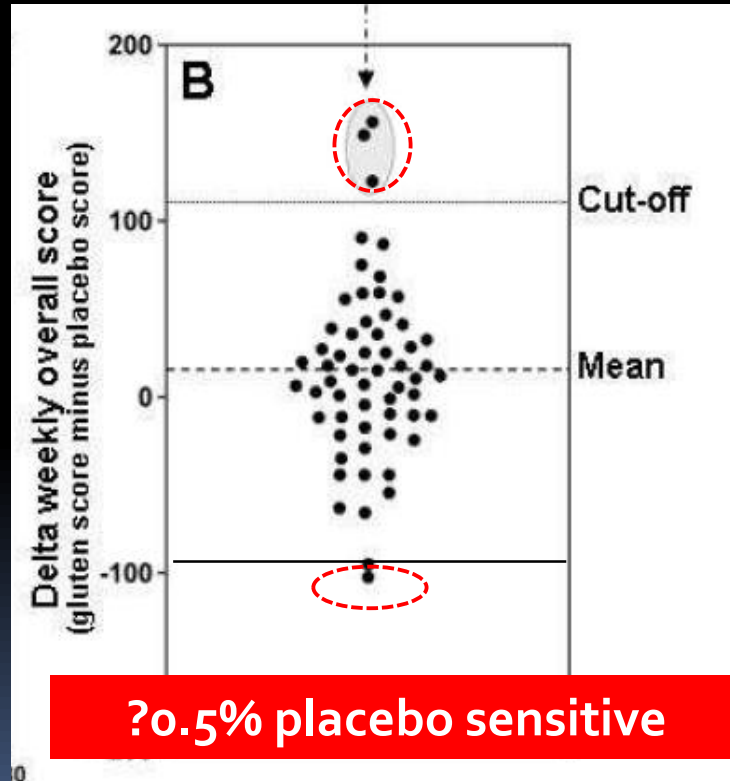


?3% placebo sensitive

Biesiekierski et al, GE 2013

? 5% gluten sensitive

Overall symptoms

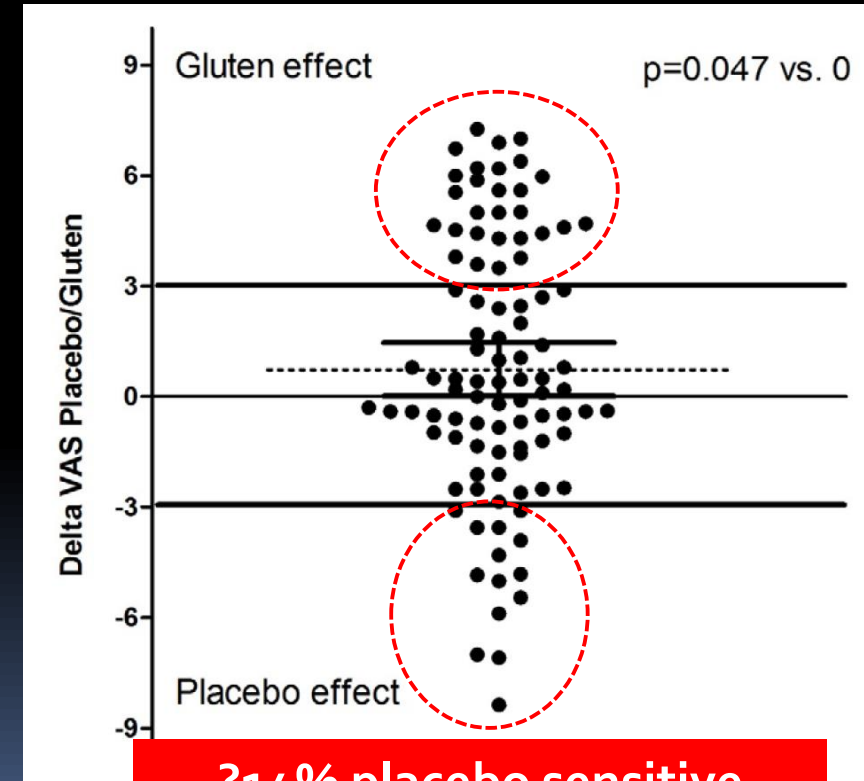


?0.5% placebo sensitive

Di Sabatino et al CGH 2015

? 28% gluten sensitive

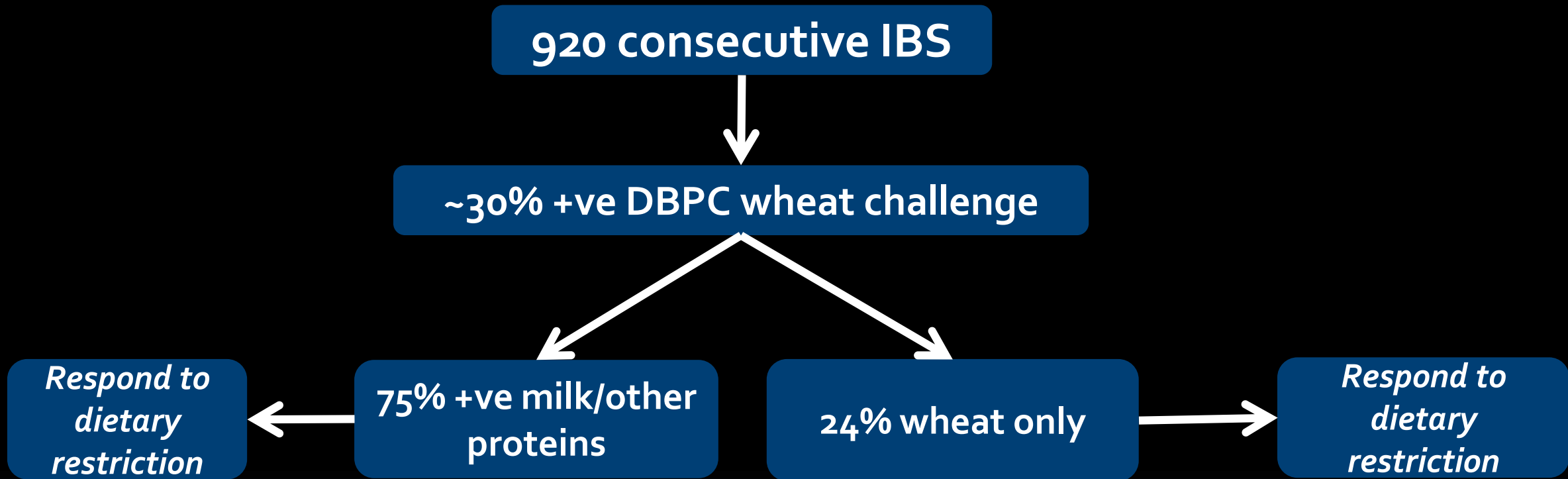
'Wellness'



?14% placebo sensitive

Eli et al Nutrients 2016

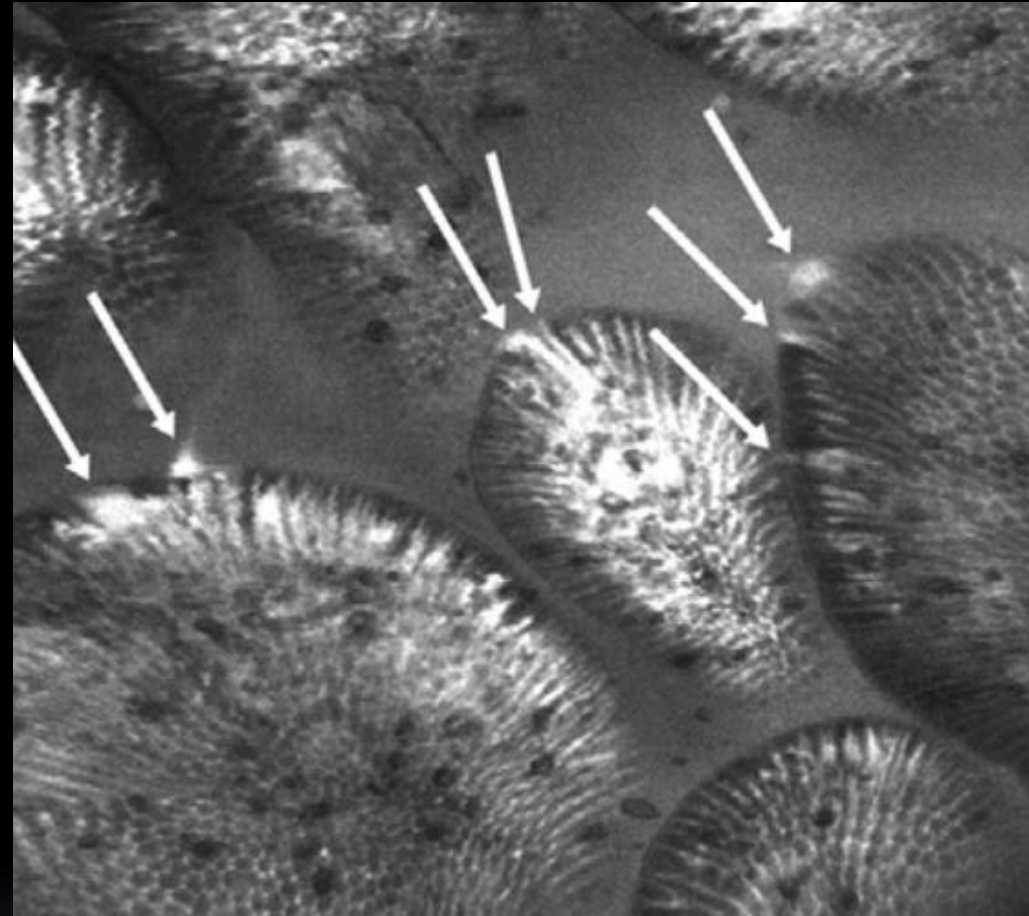
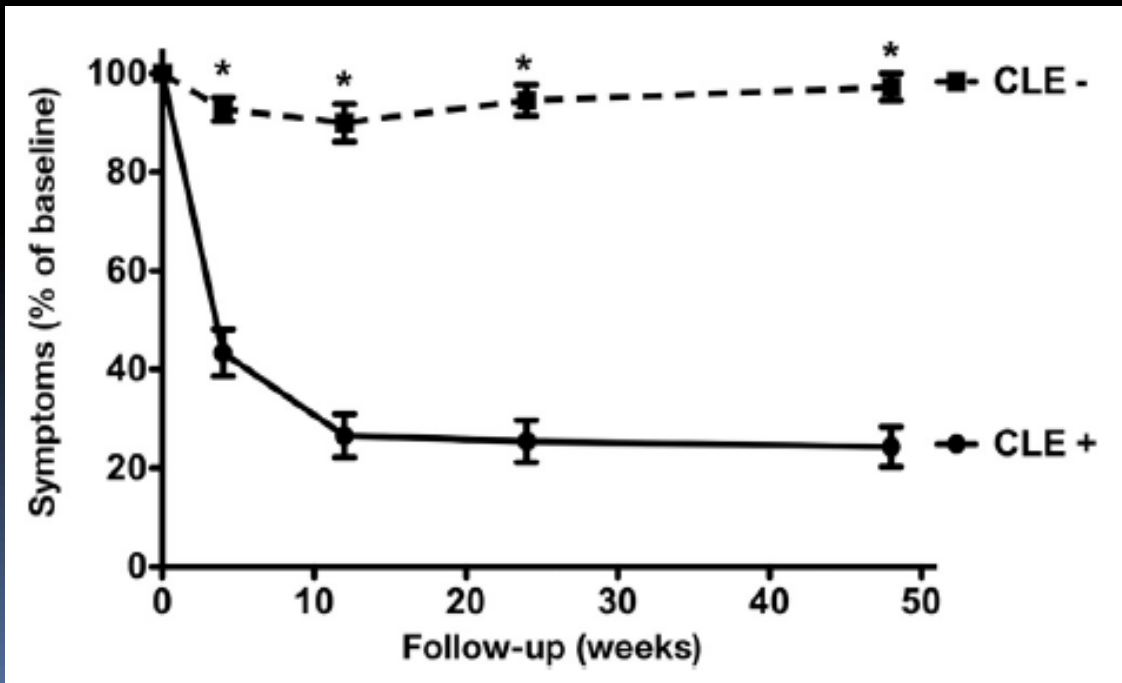
DBPC challenges in clinical practice



- 90% IELs ± eosinophils in duodenum
- 75% intra-epithelial eosinophils in colon
- 80% +ve basophil activation test

Confocal laser endomicroscopy (CLE) following food challenge


- 22/36 IBS (+ food intolerance)
→ +ve CLE lesions
 - wheat 13, milk 9, yeast 6, soy 4
- IEL count >25/100 EC in 70%



Fritscher-Ravens et al, Gastroenterology 2015




Mechanism of non-coeliac wheat intolerance?

- Majority secondary to FODMAPs
 - Nearly all have normal duodenal histology
 - Minority secondary to sensitivity (immune reactions) to wheat protein(s)
 - nearly all have abnormal duodenal histology
- 



Bioactive food chemicals


- **Huge number of chemicals in food**
 - Most are natural: e.g., salicylates, amines and glutamates
 - Food additives; e.g., glutamates, benzoates, sulfites, nitrates
 - **Multiple mechanisms by which they can induce symptoms**
 - Activate specific receptors, stimulate EC cells, activate mast cells, induce inflammation
 - **Low chemical diet approach**
 - Used widely in Australia (exclusion-multiple rechallenge methodology)
 - No biomarker to recognise those susceptible
 - Evidence for efficacy observational only
 - **Awaits proper evaluation**
- 

Risks of restrictive diets

- Impair food-related quality of life
- Encourages linear thinking re food
 - All illness is due to what you eat
 - Risk of undertreating serious illness
- Lead to nutritional inadequacy
- Precipitate eating disorders in the vulnerable
 - e.g., orthorexia nervosa
- Effect on gut microbiota
 - e.g., strict FODMAP restriction → loss of prebiotic effects of oligosaccharides
- Effect on your friends and colleagues



Dietary strategy in IBS

- Diet is only one part of multimodal strategy
 - Depend upon the clinical scenario
 - Not interested in diet, major psychological co-morbidities, at-risk of eating disorder, already on gluten-free/other restrictive diet
 - Diet to choose now
 - Low FODMAP diet
 - Strong evidence-base and well supported
 - Try to avoid strict diet long term
 - Gluten-free, low chemical, et al → poor evidence base
- 



... and beyond?

Need :

- Biomarkers to recognise those with sensitivity to dietary proteins (wheat/gluten, milk, soy)
 - More work identifying the role of food chemicals (salicylates, amines, glutamates)
 - Well designed interventional studies with quality interpretation of results
- 