



MONASH University

Medicine, Nursing and Health Sciences

A gut health approach to metabolic health.

Dr Jane Muir

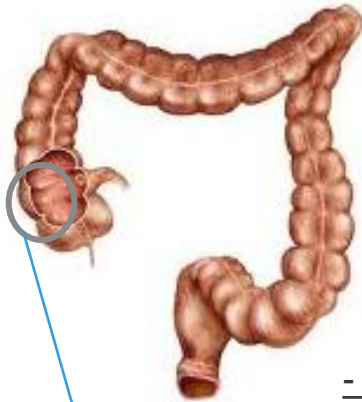
Head of Translational Nutrition Science

Department of Gastroenterology, Central Clinical School



RAPIDLY CONVERGING AREAS:

Gut microbiology, nutrition and immunology & pharmacology.



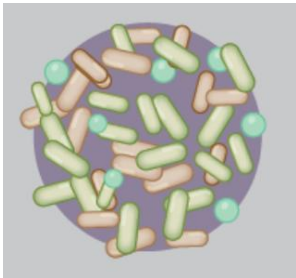
-TRP receptors

-Short chain fatty acids

-Gas

- Gut inflammation
Cytokines (eg. IL-6)

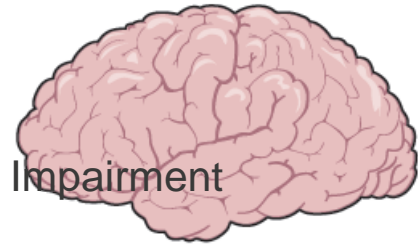
Gut microbiota



-Pain

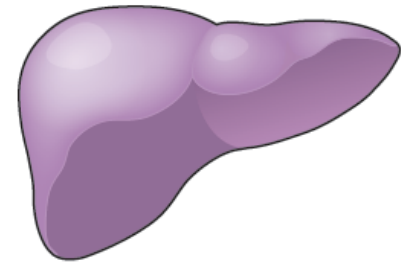
-Cognitive Impairment

- fatigue



Inflammatory cells

GPR43- receptors



SCFA

Inflammation

- fatigue



Gastrointestinal Tract- Clinical Problems-

CHRONIC INFLAMMATION

Functional gastrointestinal disorders (FGID) – incl IBS

15%

Colorectal cancer

5%

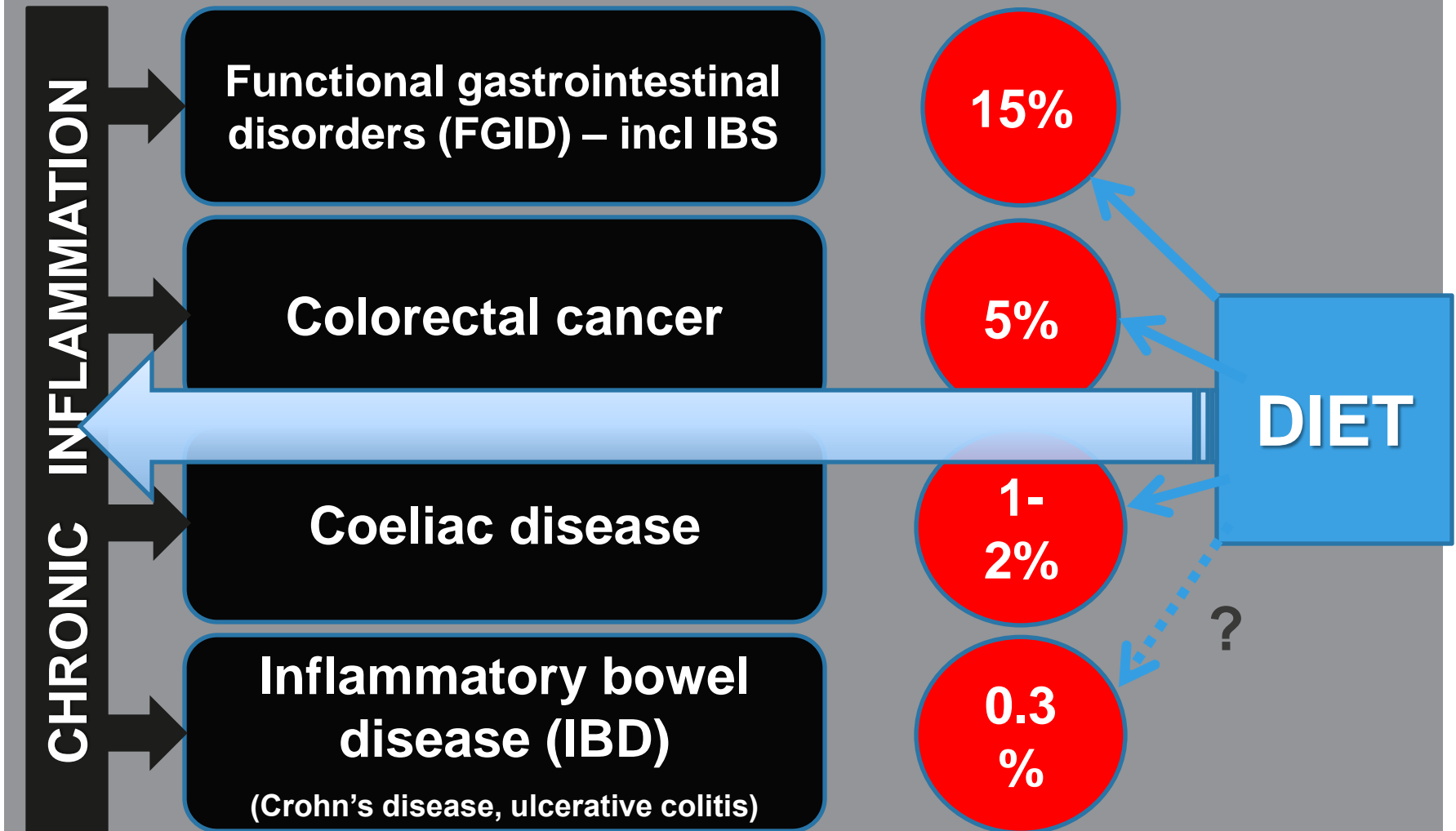
Coeliac disease

1-2%

Inflammatory bowel disease (IBD)
(Crohn's disease, ulcerative colitis)

0.3%

Gastrointestinal Tract- Clinical Problems-



Core questions: Can events occurring in the gut impact on systemic events ?

1. PAIN- Can we use diet to relieve symptoms (eg. pain) associated with gut disorders/disease?
2. GUT INFLAMMATION: Can events occurring in the gut (inflammation) - impact on other metabolic events?
3. GUT INFLAMMATON: How to treat inflammation in the gut?
4. GUT microflora: Can we use diet to control the type of bacteria that grows in our bowel?

PAIN:

1. Can we use diet to relieve gut symptoms?

Major symptoms associated with functional bowel disorders (“Irritable bowel syndrome -IBS”)

- Chronic – e.g., >3 months in the year
- Abdominal pain or discomfort
- Disturbed bowel habits
- Abdominal bloating

FODMAPs = poorly absorbed short-chain carbohydrates

XS Fructose

Lactose

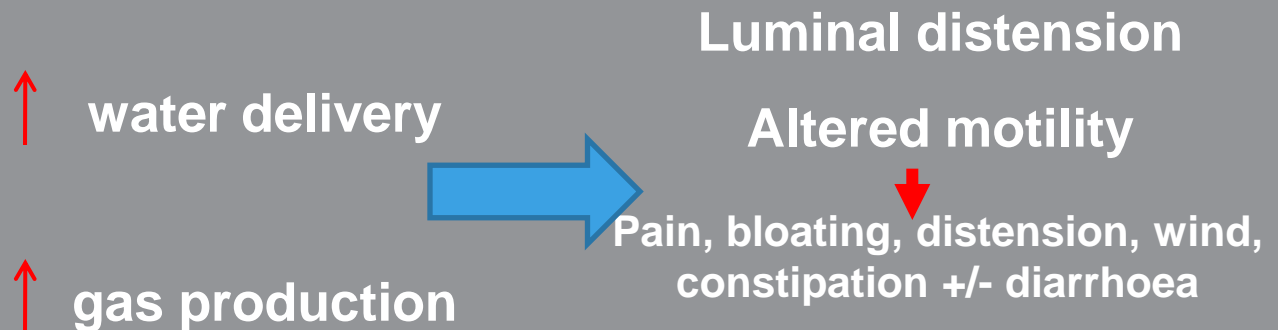
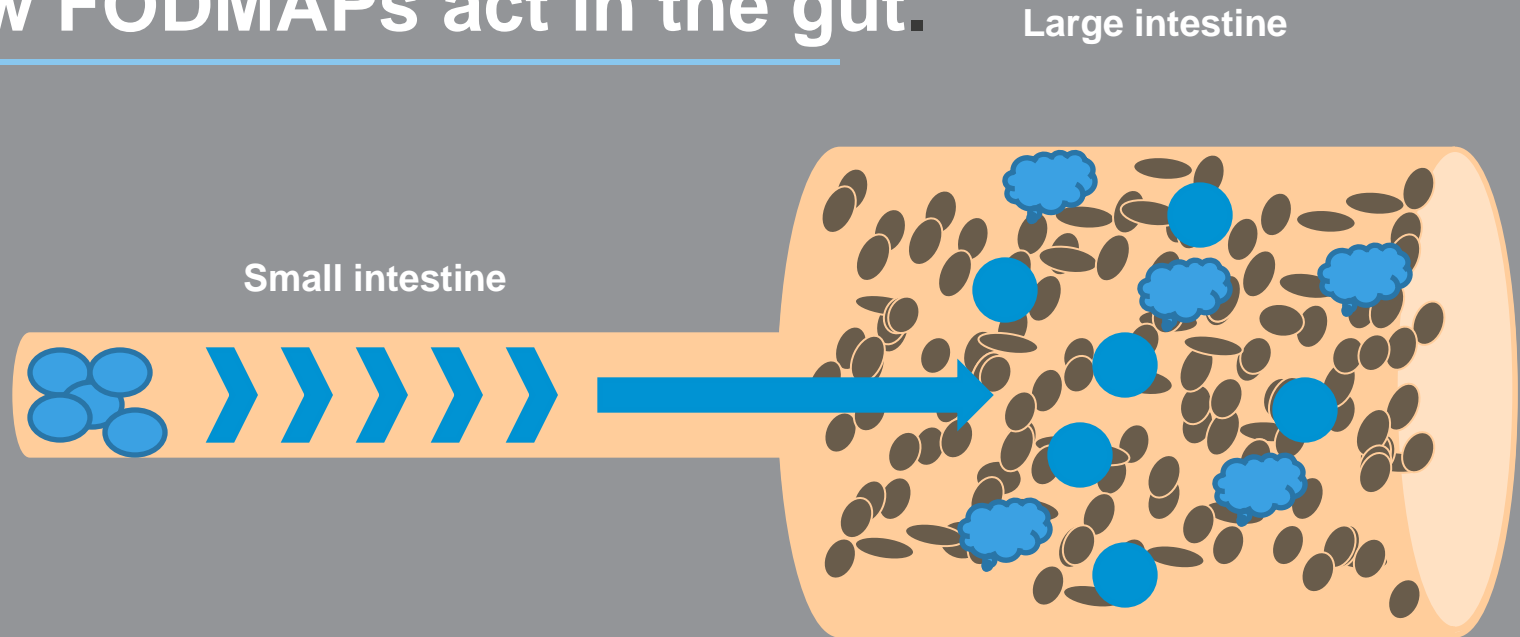
Fructans

GOS

Polyols



How FODMAPs act in the gut.



What are the causes of IBS?

- GI infection → post-infectious IBS
- Stress &/or how it is handled
- Altered (disturbed) gut microflora.
- Hypersensitivity of the gut to luminal distension [*Enteric Nervous System (ENS)*].



Enteric nervous system

Controller of most GI functions - secretion, motility, blood flow, mucosal growth

luminal distension

“Normal” low intensity stimuli

- Little effect on motility
- Few conscious messages

“Abnormal” high intensity stimuli

- Alter motility
- Pain, discomfort, awareness

IBS

PAIN REDUCTION:

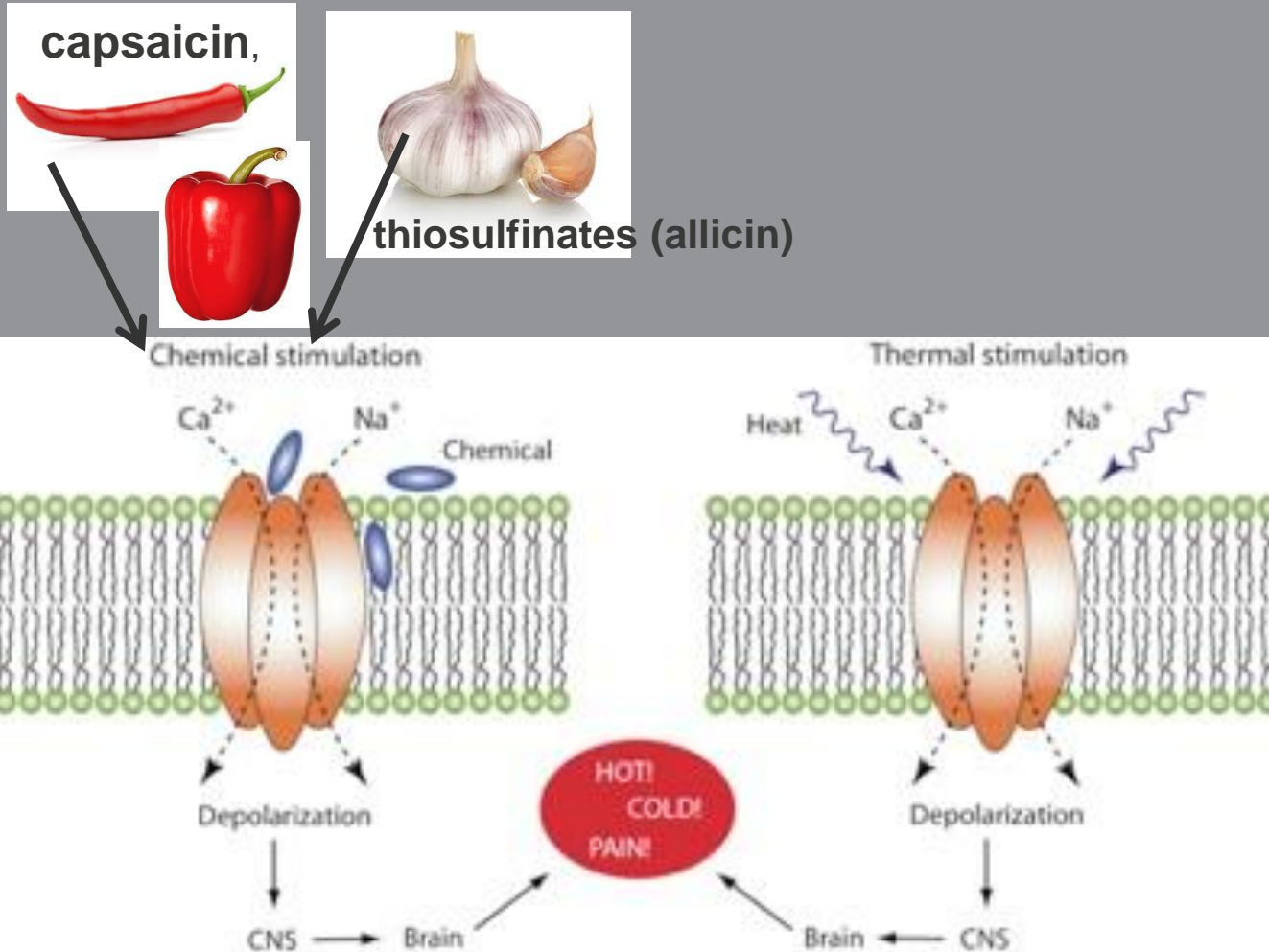
Low FODMAP diet acts on luminal distension
(less gas, less water motility)



PAIN- new pathways and other dietary factors involved with pain



TRP receptors (cation channels): Key receptors in pain-sensing



Inflammation:

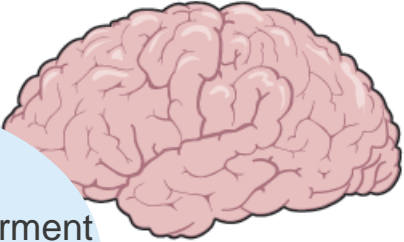
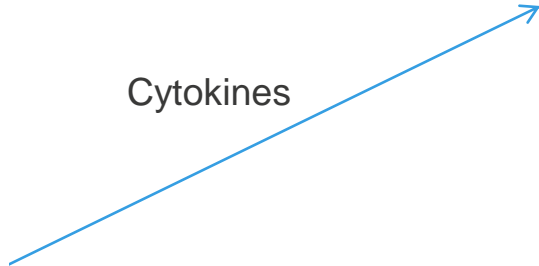
2. Can events occurring in the gut impact on other metabolic events?

Gut Inflammation: Systemic Events



Inflammation

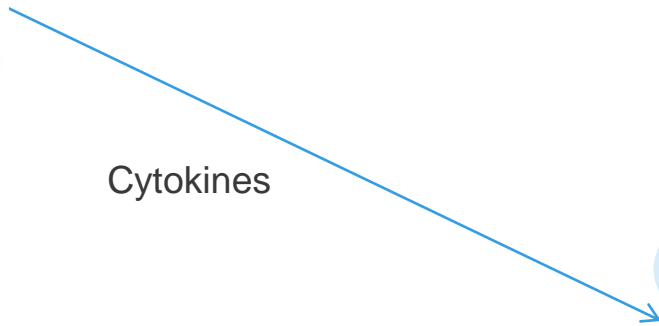
Cytokines



Inflammation
-Cognitive Impairment
- fatigue

A light blue oval containing text, positioned next to a pink illustration of a human brain.

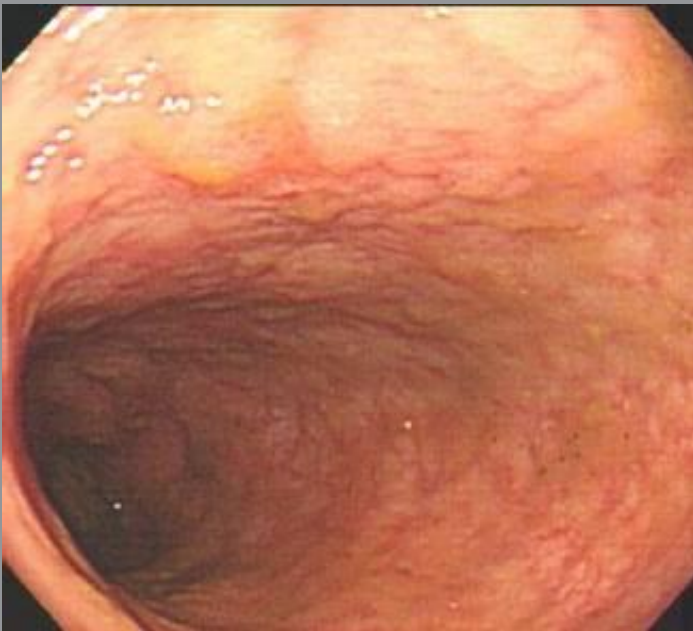
Cytokines



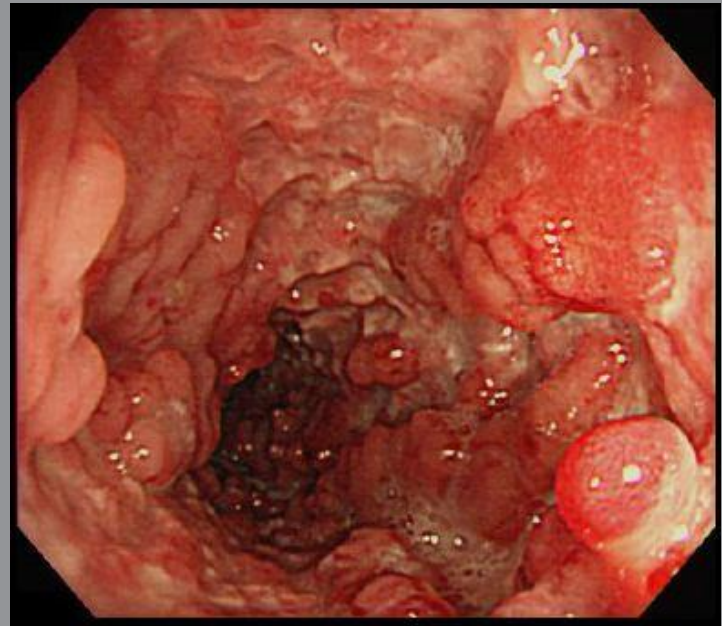
- Inflammation
- fatigue

A light blue oval containing text, positioned above a red illustration of a muscle.

GUT INFLAMMATION: Inflammatory bowel disease



Healthy mucosa



Inflammation- Crohn's (CD),
Ulcerative colitis (UC)

2. Gut Inflammation: Effects on cognitive dysfunction and fatigue.

Daniel Van Langenberg, Greg Yelland, Peter Gibson

DR van Langenberg, PR Gibson. Systematic Review: Fatigue in inflammatory bowel disease. *Aliment Pharm Ther* 2010; 32 (2): 131–143.

G Morrison, **DR van Langenberg**, SJ Gibson, PR Gibson. Chronic pain in inflammatory bowel disease: characteristics and associations in a hospital-based cohort. *Inflamm Bowel Dis* 2012 [submitted, under review]

DR van Langenberg, P Della Gatta, B Hill, S A Warmington, D K Kidgell, PR Gibson, AP Russell. Identification of molecular factors regulating skeletal muscle mass and function in patients with Crohn's disease. *Clin Gastro Hepatol* 2012

How we measure changes in cognition: The SCIT

the **Subtle Cognitive Impairment Test**

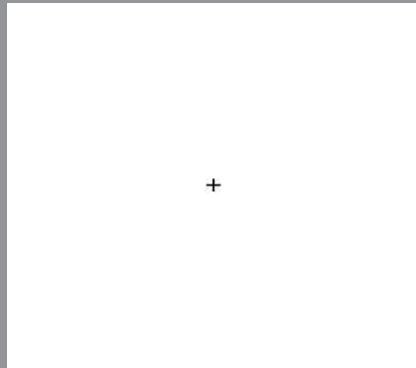
- **Simple computer based cognitive test**
 - 7 minute tutorial
 - 5 minutes to administer
- Designed to detect subtle cognitive impairment
- **Highly reproducible**
- **Not subject to practice effect**⁴



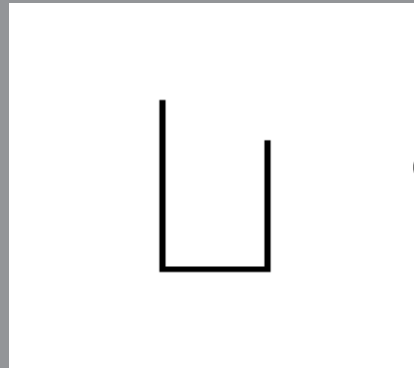
⁴ Friedman et al, *Int J Geriatr Psychiatry* 2012

U-Stimulus & Mask

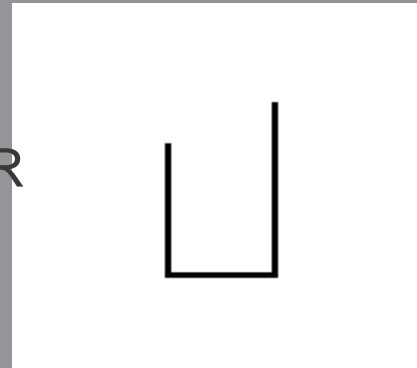
1. Fixation stimulus



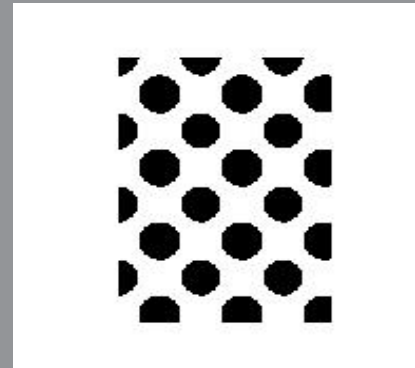
2. Test stimuli

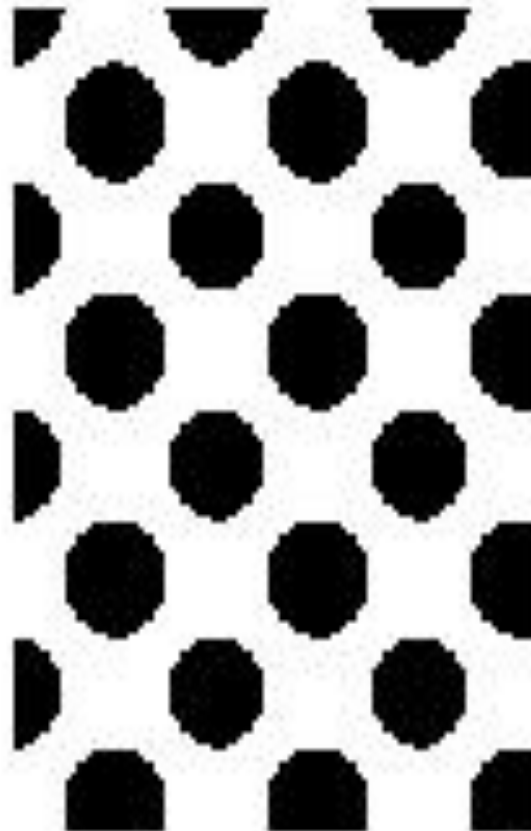


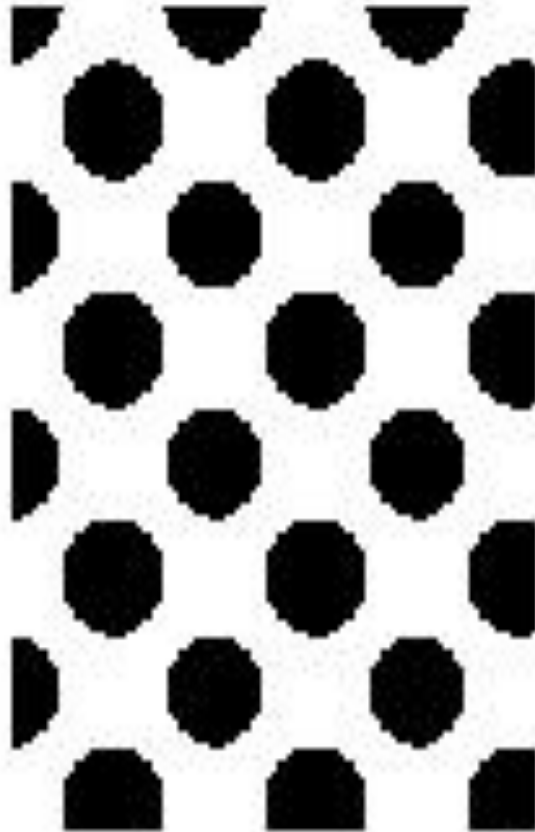
OR



3. Mask



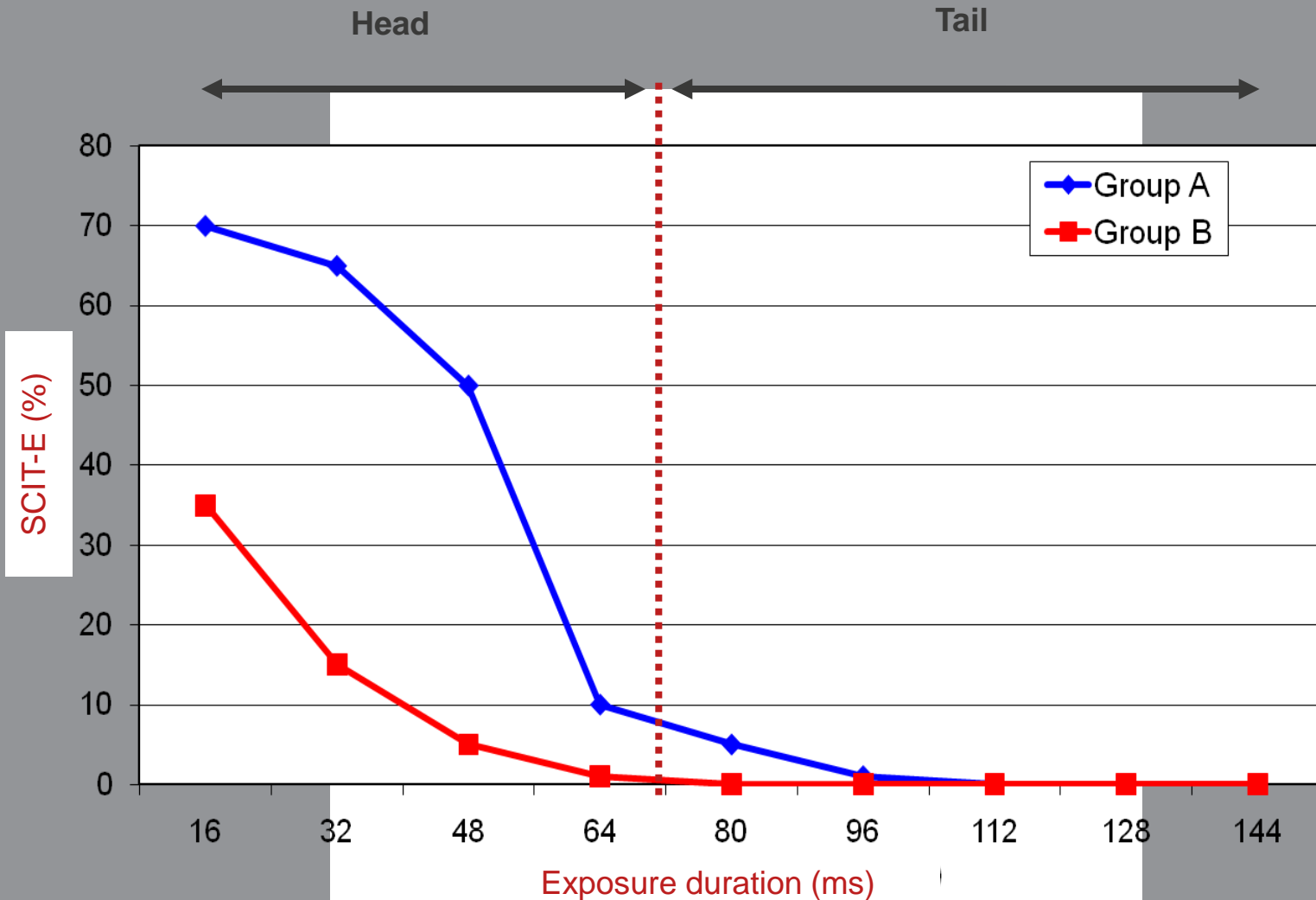




Outcome measures

- **Error rate** at each exposure duration $\frac{\text{Number of errors made}}{\text{Number of trials presented}}$
- **Response Time** (mean, milliseconds) at each exposure duration

Example-How we measure changes in cognition: SCIT (Greg Yelland).



Slower response time in Group A

Fatigue in Crohn's disease

Physical

Subjective:

weakness, inability to complete/initiate task

Objective:

measurable decrease in performance with repeat/prolonged activity

Cognitive

Subjective:

difficult concentrating, thinking clearly

Objective:

measurable decrease in cognitive function or performance (eg SCIT)

Affect

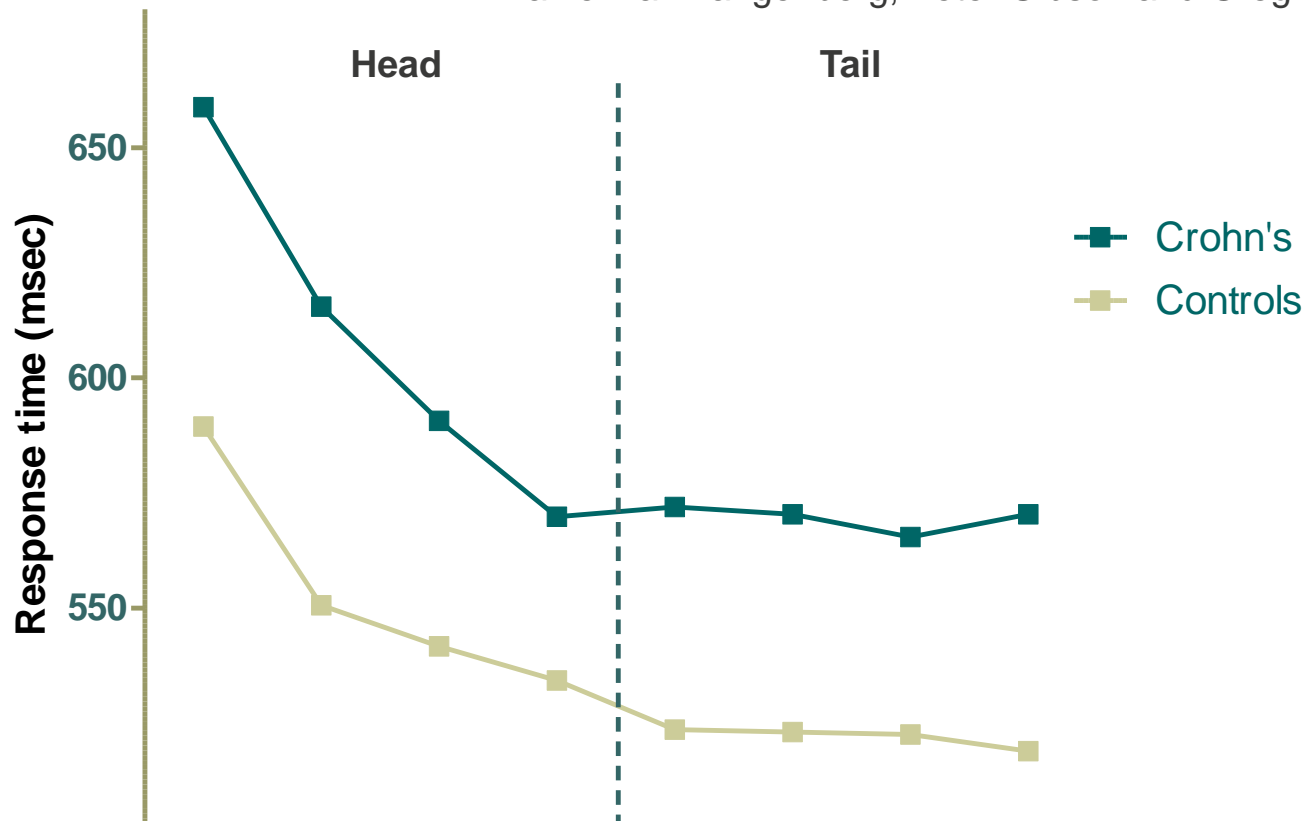
Subjective

decreased motivation, low mood, no energy

Daniel Van Langenberg, Greg Yelland, Peter Gibson

Crohn's disease vs Controls

Daniel Van Langenberg, Peter Gibson and Greg Yelland



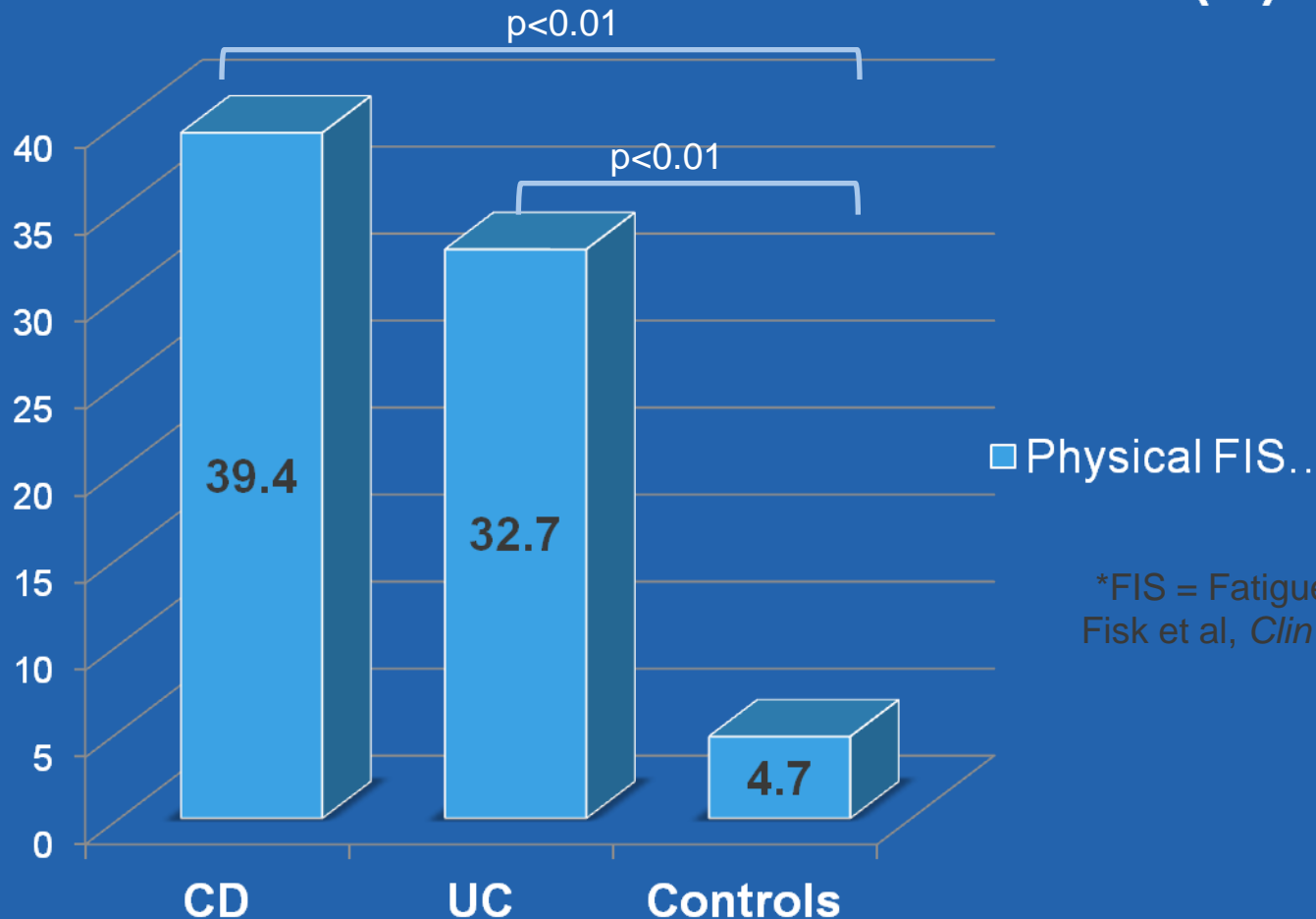
Slower response time in Crohn's subjects across all response times

2. Gut Inflammation: Effects on fatigue.

Daniel Van Langenberg, Peter Gibson

Fatigue in IBD:

Prevalence in Australian IBD clinic (%)



*FIS = Fatigue Impact Scale
Fisk et al, *Clin Infect Dis* 1994

Muscle force and fatigue in CD vs Healthy:

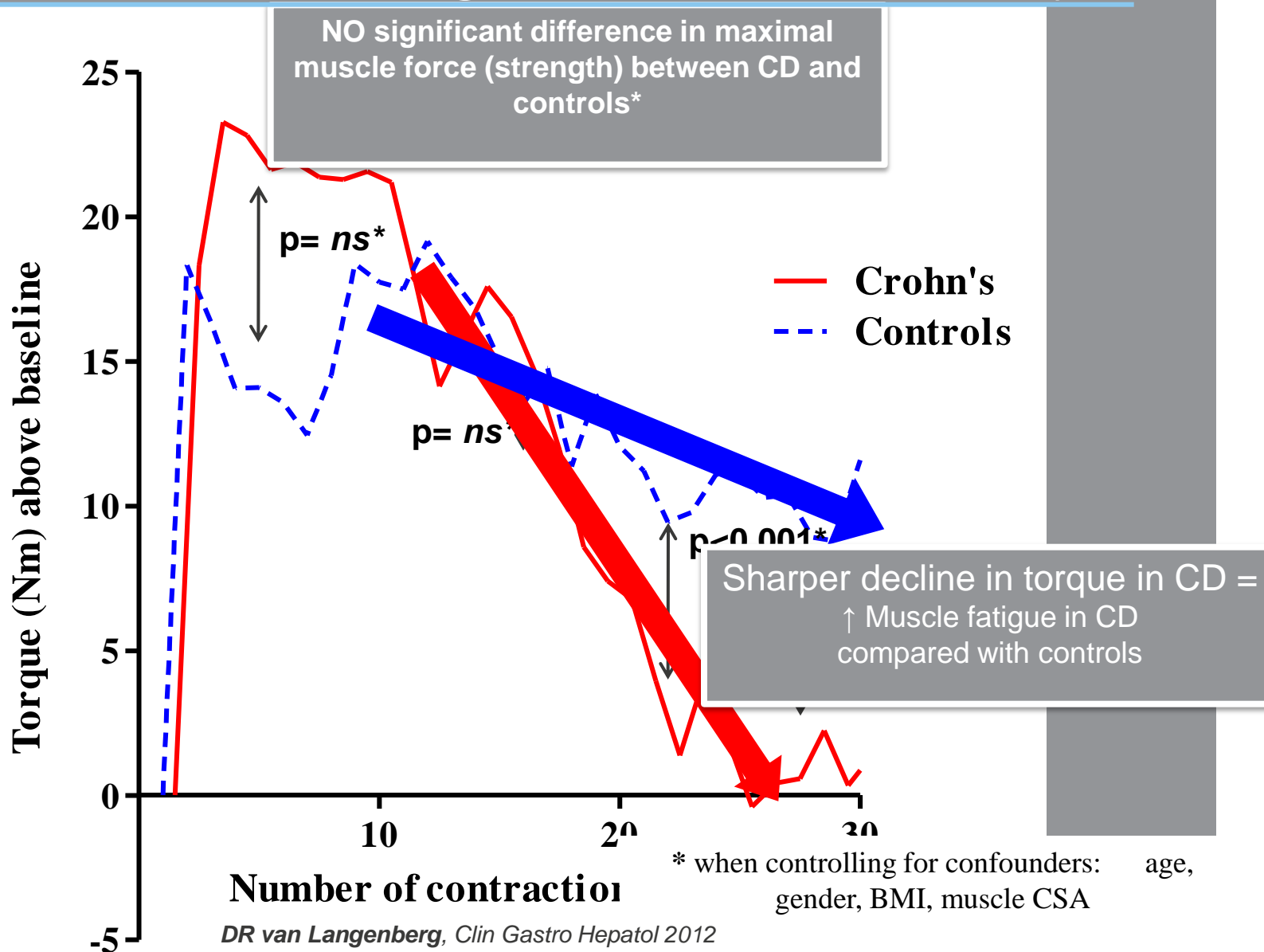
Methods:

- Quadriceps muscle
- Technician blinded to status of participant
- 5 minute exercise protocol



*DR van Langenberg, P Della Gatta, B Hill, S A Warmington, D K Kidgell, PR Gibson, AP Russell.
Identification of molecular factors regulating skeletal muscle mass and function in patients with Crohn's
disease. Clin Gastro Hepatol 2012*

Muscle force and fatigue in CD vs Healthy:



Number of contraction

DR van Langenberg, Clin Gastro Hepatol 2012

2. Gut inflammation: Muscle fatigue in IBD. Possible causes.

In Crohn's patients-

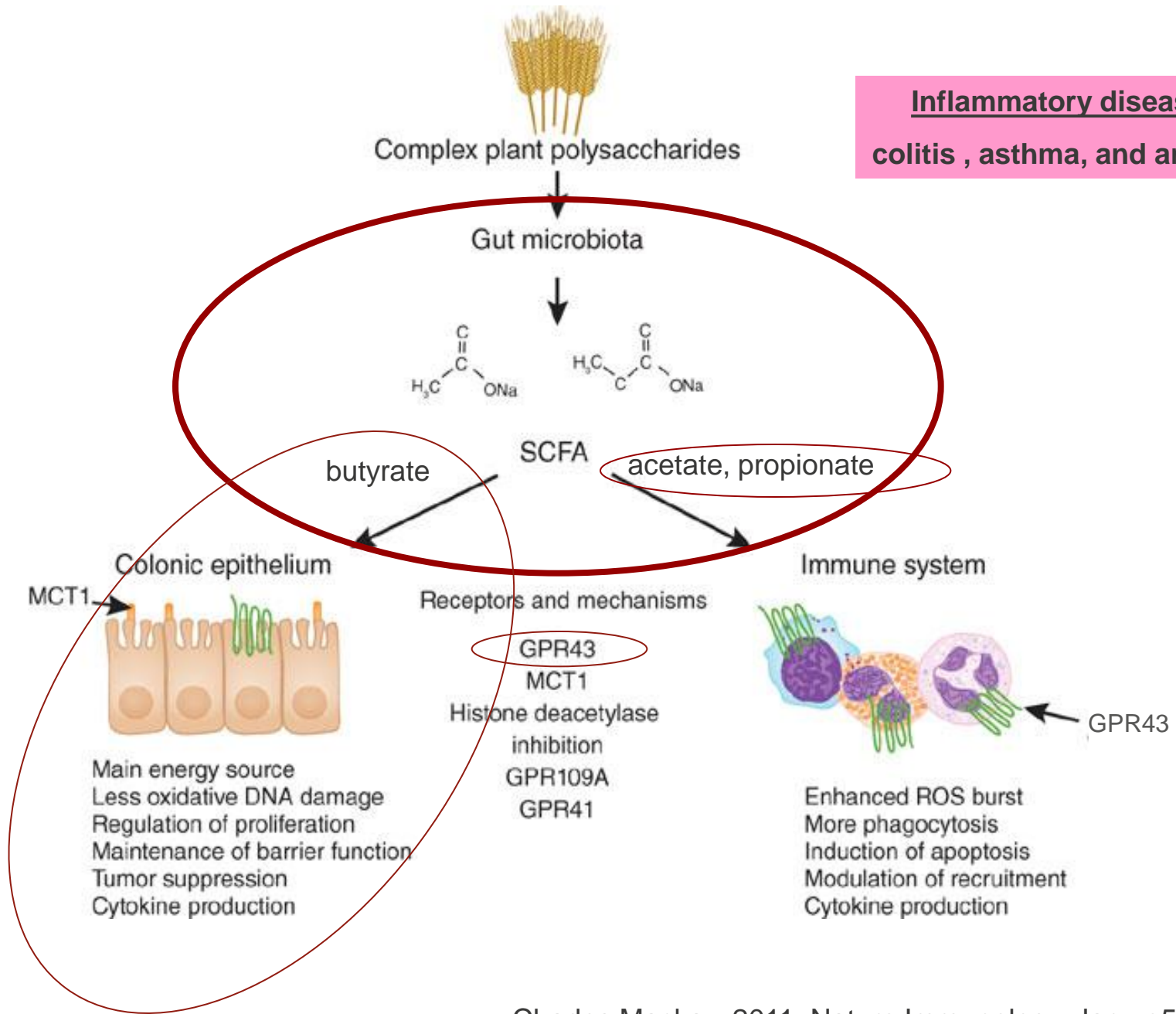
- Raised pro-inflammatory IL-6 cytokines
- Lowered lower serum Vitamin D3
- Lower serum Mg

It is important for inflammation to be controlled as this may have systemic effects for that individual

*DR van Langenberg, P Della Gatta, B Hill, S A Warmington, D K Kidgell, PR Gibson, AP Russell.
Identification of molecular factors regulating skeletal muscle mass and function in patients with Crohn's
disease. Clin Gastro Hepatol 2012*

3. Gut Inflammation IBD: How to treat inflammation in the gut?

**Inflammatory diseases:
colitis , asthma, and arthritis.**



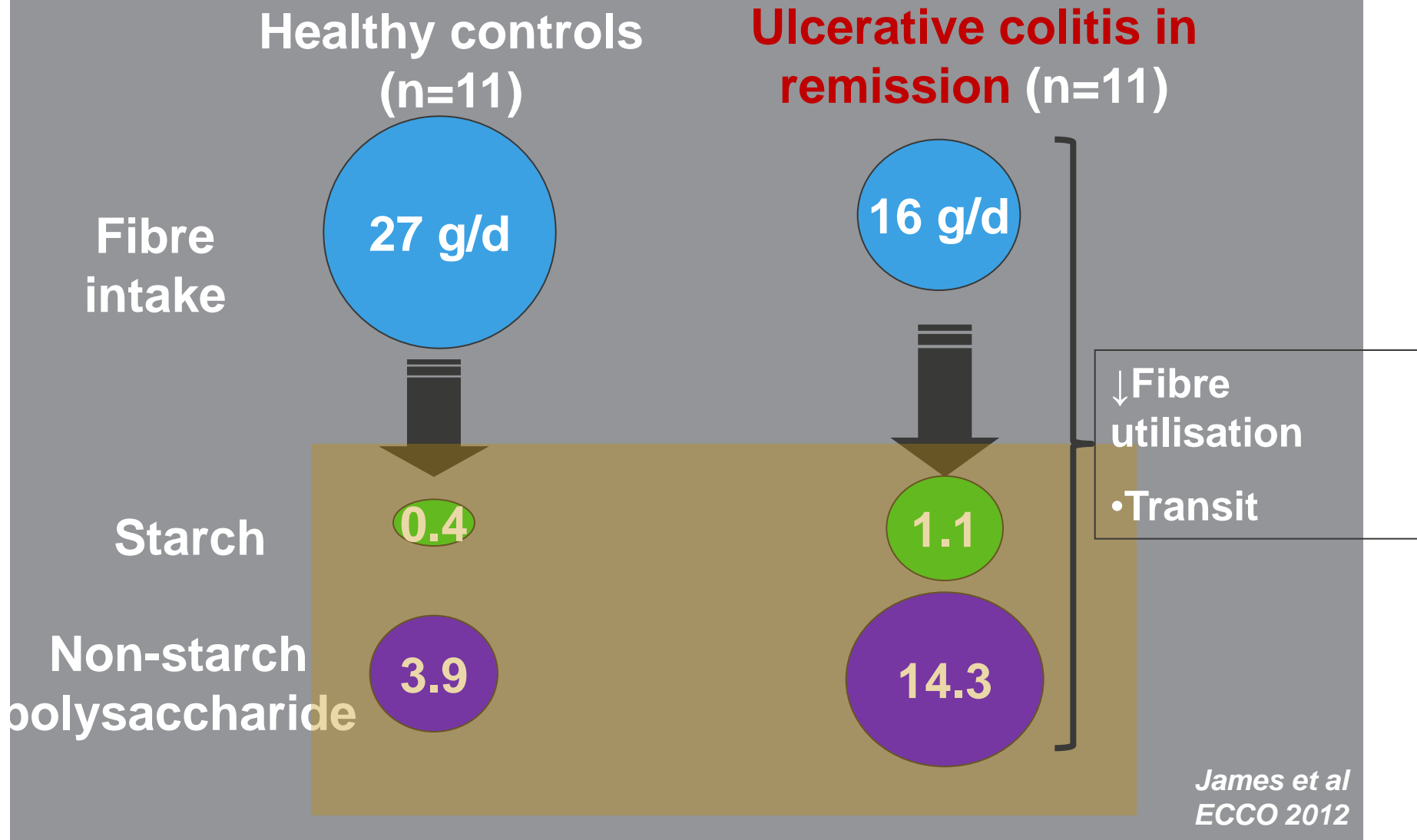
How do we generate SCFA?

-Bacterial metabolism of Dietary Fibre

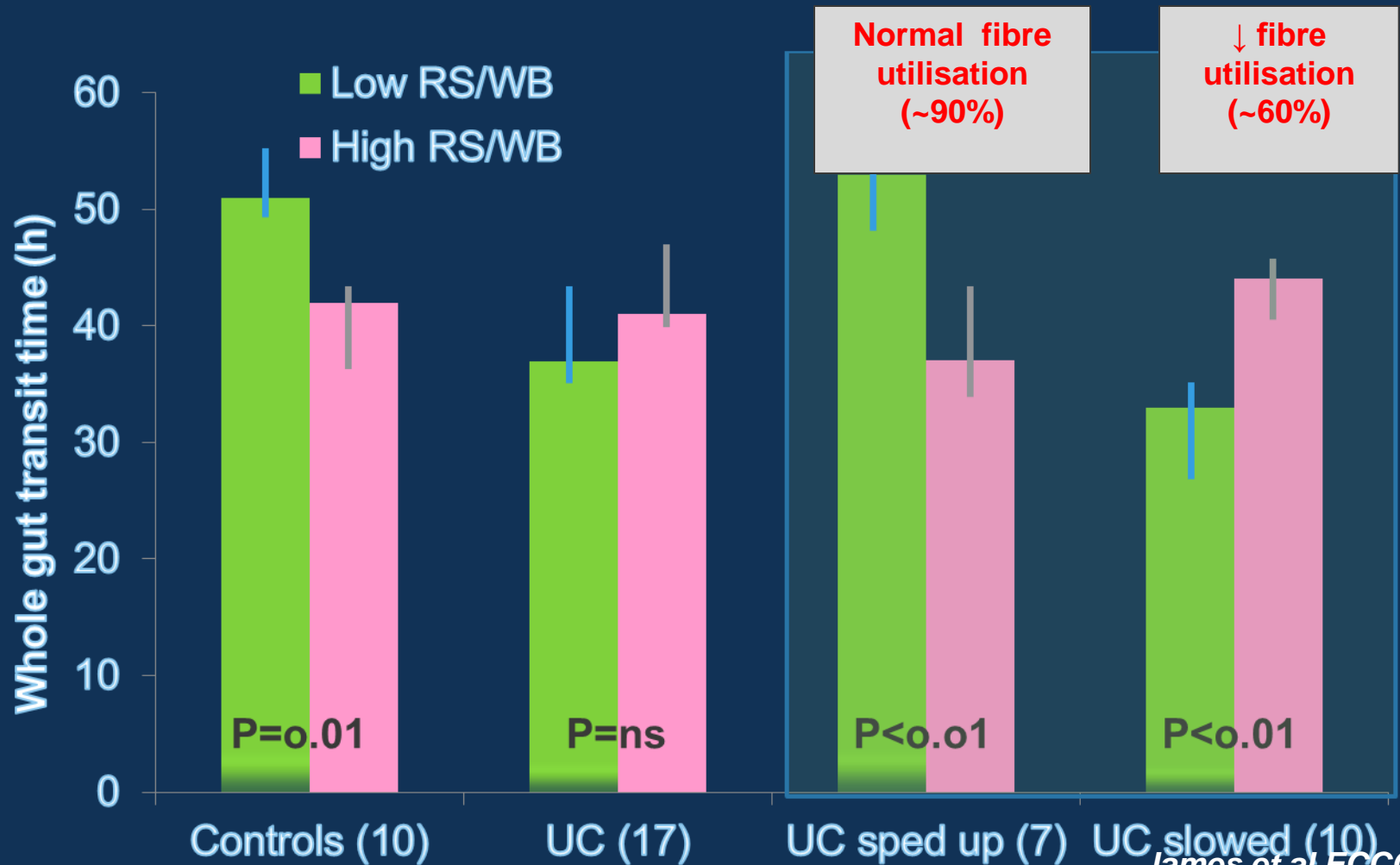
Different fibre types have different effects- in a healthy gut.

Dietary fibre utilization and transit time in Healthy and patients with IBD (in remission).

Healthy vs IBD: Input-output on usual diet



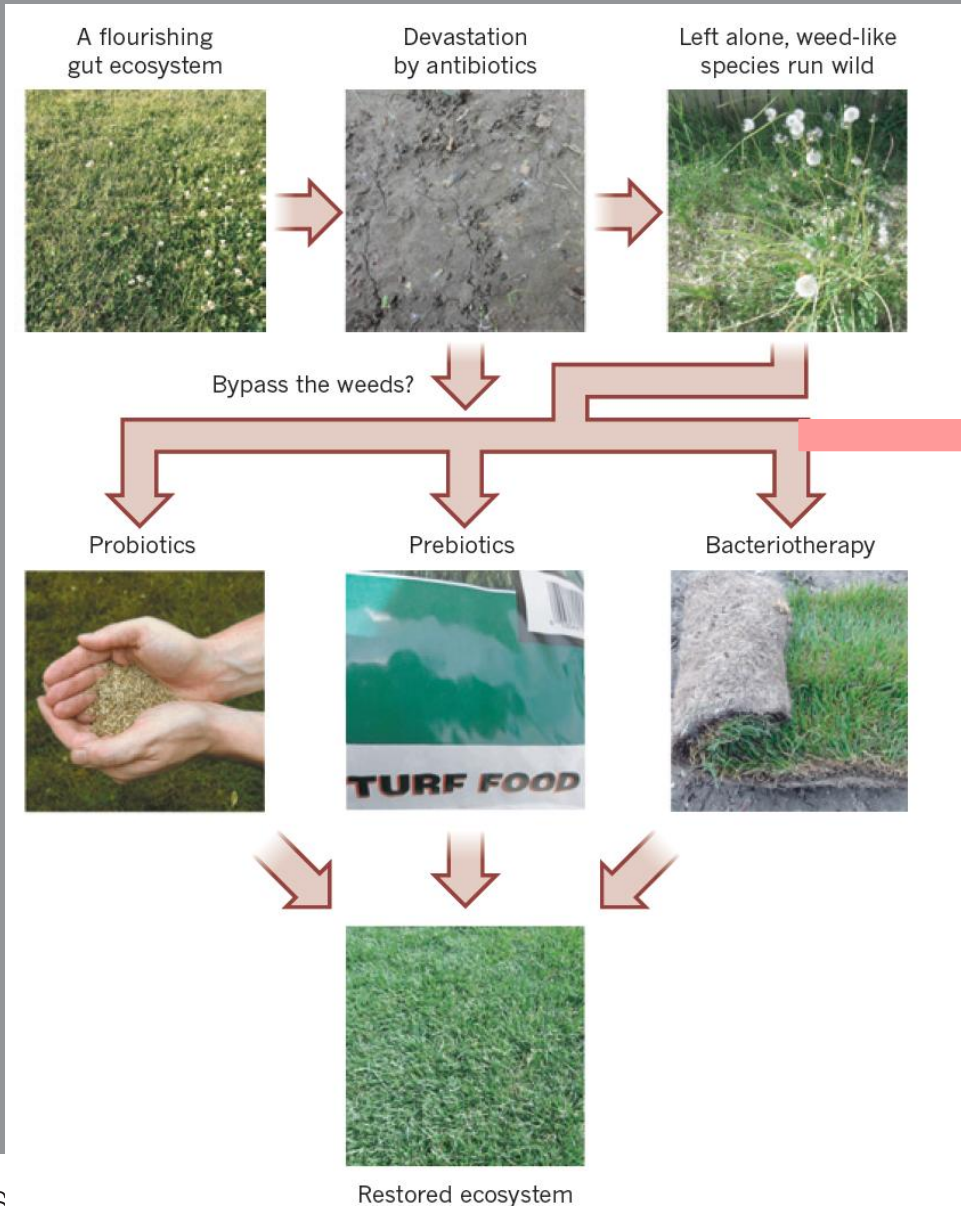
IBD Patients (in remission): Effect of adding RS (15g)+ wheat bran (12g/d) on whole gut transit time



3. Can we use diet to control the type of bacteria that grows in our bowel?

Yes we have recently shown this.

How to change gut microflora



Problem with our low FODMAP diet- it reduces the intake of natural dietary prebiotics

Low FODMAP



High FODMAP

- fructans, GOS, polyols



Long-term effects of restricting FODMAP carbohydrates:

Emma Halmos
(Dietitian and PhD candidate)

Potential health benefits of FODMAPs

- Substrates of bacterial fermentation → SCFA
 - **Butyrate** → important for colonic health (ant inflammatory & anticarcinogenic)
- Prebiotics (GOS, fructans) → selectively promote growth of 'good' bacteria → putative health benefits
 - e.g.,
 - Bifidobacteria
 - Butyrate-producing bacteria (*F. prausnitzii*, *C. coccoides*)

The low FODMAP diet may have an impact on these

Potential 'downside' of the Low FODMAP diet

- Staudacher et al (King's College Group)- With low FODMAP diet showed improved symptoms in IBS patients over 4 weeks. However, lower numbers of *bifidobacteria* with low FODMAP diet in patients with IBS. (ref. Staudacher et al Journal of Nutrition, 2012;142;1510-8.)
- Halmos et al (Monash University Group) -Showed improvements in symptoms in IBS patients over 3 weeks on the low FODMAP diet. However, on the low FODMAP diet, proportion of 'good' bacteria decreased- *Bifidobacteria* and Butyrate-producing (*F prausnitzii*, *C. coccoides*). (manuscript in preparation)

Summary: Gut, diet and systemic events

- 1. PAIN- Can we use diet to relieve symptoms (eg. pain) associated with gut disorders/disease?**
 - Low FODMAP diet reduces abdominal pain associated with IBS
- 2. GUT INFLAMMATION: Can events occurring in the gut (inflammation) - impact on other metabolic events?**
 - Cognitive function and muscle fatigue can be reduced with inflammation (via cytokines IL-6)
- 3. GUT INFLAMMATON: How to treat inflammation in the gut?**
 - SCFA produced by bacteria fermentation of undigested CHO may be important. Butyrate local effects, acetate and propionate systemic effects.
- 4. GUT microflora: Can we use diet to control the type of bacteria that grows in our bowel?**
 - Bifido bacteria and butyrate-producing may be manipulated by FODMAP (natural prebiotics) intake

The Monash team: Peter Gibson, Jaci Barrett, Emma Halmos, Jessica Biesierkierski, CK Yao, Kelly Liels, Debbie King, Vicki Power, Sue Shepherd, Jessie Mills, Nia Rosella, Rosemary Rose, Richard Gearry, Peter Irving, Sally James, Debbie Nathan, Melissa Haines, Evan Newnham, Catherine Croagh, Daniel van Langenberg, Derrick Ong, Shaylyn Mitchell,

CSIRO: Dr Tony Bird, Dr Claus Christophersen

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