Stress in de Buik:
de Wisselwerking tussen Brein en Darm

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TARGID, KULeuven

Stress

- Aspecifiek antwoord van het lichaam op een schadelijke prikkel.
- Reactie van het lichaam op een verstoring van de homeostase
- Gevoel van verlies van voorspelbaarheid en controle.

'Just as feelings of comfort and peace of mind are fundamental to normal digestion, so discomfort and mental discord may be fundamental to disturbed digestion.'

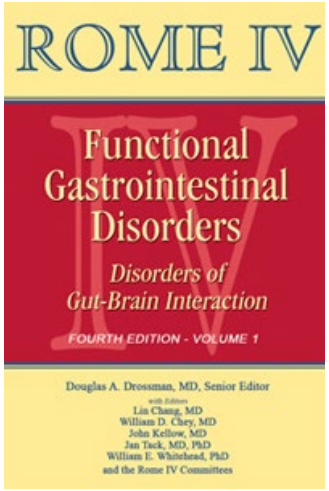
Maagdarmklachten, IBS



Walter B. Cannon

Selye et al. Nature 1936
Chrousos et al. Nat Rev Endocrinol 1939
Koolhaas et al. Neurosci Rev 2011

Prikkelbare Darm Syndroom: Rome IV



Terugkerende abdominale pijn >1 dag/week in de voorbije 3 maanden

\+ minstens 2 van 3 criteria:

- **Verband met defaecatie**
- **Geassocieerd met verandering in frequentie van defaecatie**
- **Geassocieerd met verandering van vorm van stoelgang**

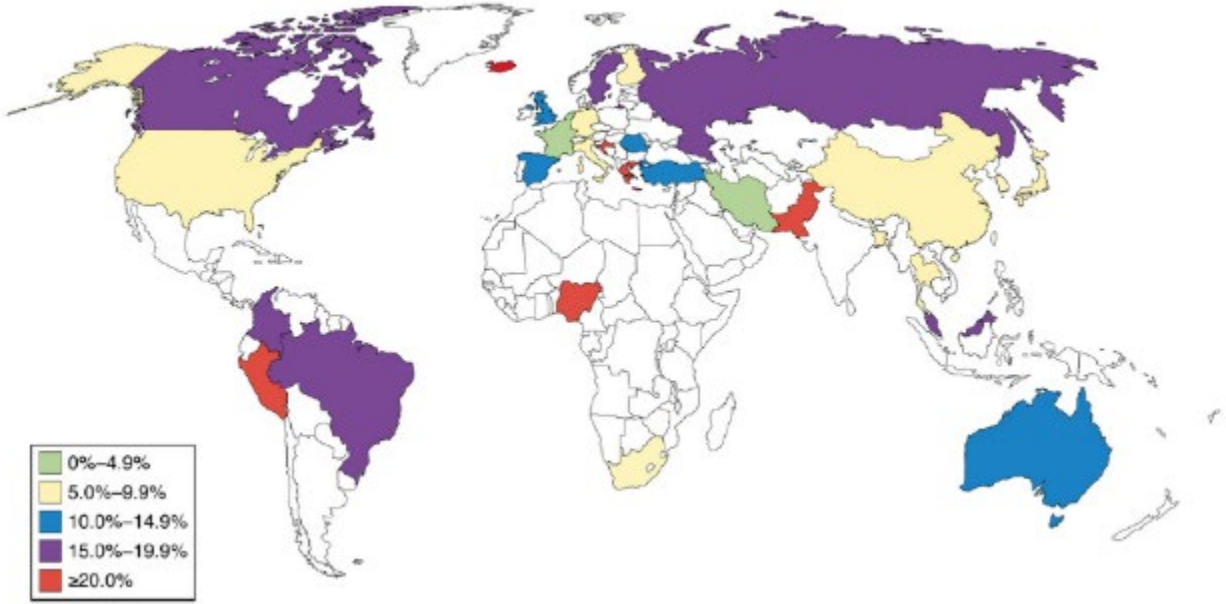
Aanwezig in de laatste 3 maanden en eerste klacht minstens 6 maanden voor diagnose

\+ Geen organische verklaring voor de klachten van de patiënt

Lacy et al. Gastroenterology 2016

Irritable Bowel Syndrome

- Frequent: 5-15% prevalentie



Lovell et al. Clin Gastroenterol Hepatol 2012

Irritable Bowel Syndrome

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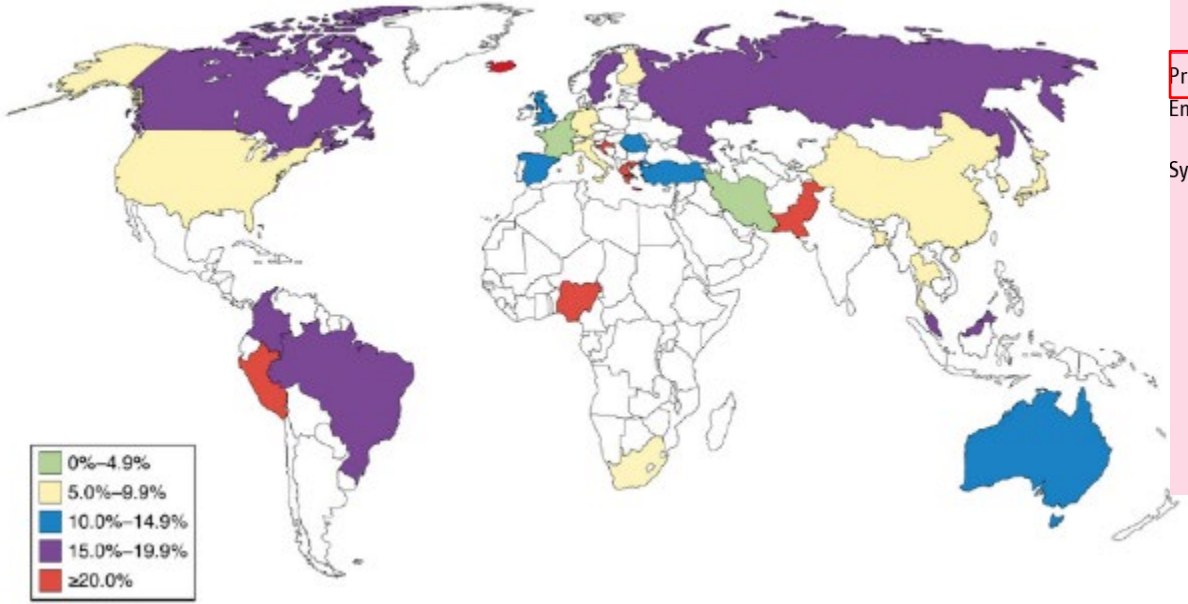


Lovell et al. Clin Gastroenterol Hepatol 2012

Internet vragenlijst bij 1012 Belgen:

	IBS according to Rome IV	Self-reported IBS
Prevalence	5.5%	17.6%
Employment state:		
Employed	63%	45%
Symptoms		
Diarrhea	37%	39%
Constipation	34%	35%
Alternating stool pattern	28%	28%
Abdominal pain	100%	48%
Bloating	74%	65%
Abdominal cramps	69%	51%
Problems with frequency of bowel symptoms	49%	27%
Problems with consistency of bowel movements	37%	24%

Van Den Houte et al. UEG Journal 2018

Irritable Bowel Syndrome

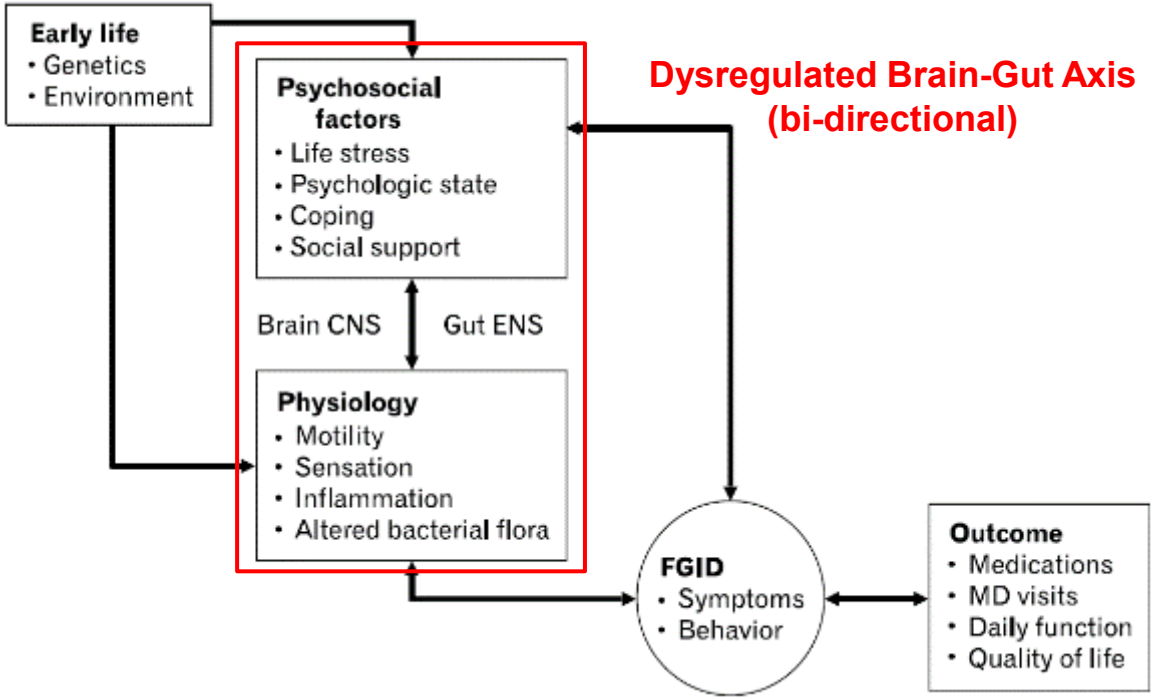
- Frequent: 5-15% prevalentie
- Eén van de meest voorkomende diagnoses in de klinische praktijk, ook bij de huisarts (tot 30% van de gastro-intestinale diagnoses bij de huisarts)
- Overwegend vrouwelijke patiënten

	No. of subjects	Pooled prevalence of IBS (95% CI)	Odds ratio for IBS (95% CI)
Age band (*y*)			
<30	6909	11.0 (6.0–18.0)	1.00
30–39	7247	11.0 (7.0–16.0)	1.04 (0.85–1.27)
40–49	7543	9.6 (6.0–14.0)	0.86 (0.59–1.24)
50–59	5434	7.8 (5.0–11.1)	0.68 (0.40–1.17)
≥60	5540	7.3 (4.3–11.0)	0.63 (0.38–1.04)
Gender			
Male	78,913	8.9 (7.3–10.5)	1.00
Female	83,330	14.0 (11.0–16.0)	1.67 (1.53–1.82)
Socioeconomic status			
High	866	14.0 (9.0–19.0)	1.00
Medium	1732	14.0 (8.0–22.0)	1.02 (0.72–1.44)
Low	2663	13.0 (7.0–22.0)	0.99 (0.71–1.36)



Thompson et al. Gut 2002
Lovell et al. Clin Gastroenterol Hepatol 2012

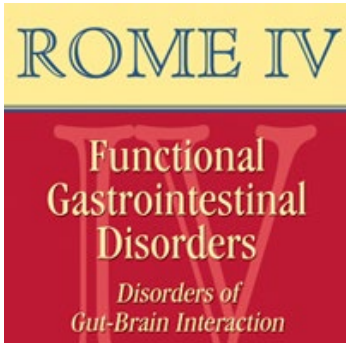
Irritable Bowel Syndrome



Dysregulated Brain-Gut Axis (bi-directional)

Functionele Gastro-Intestinale Aandoeningen
FGID

Disorders of Gut-Brain Interaction
DGBI

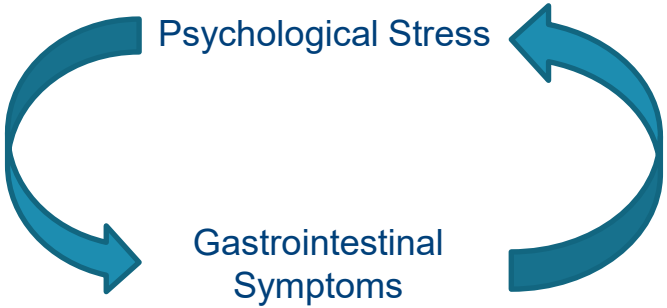


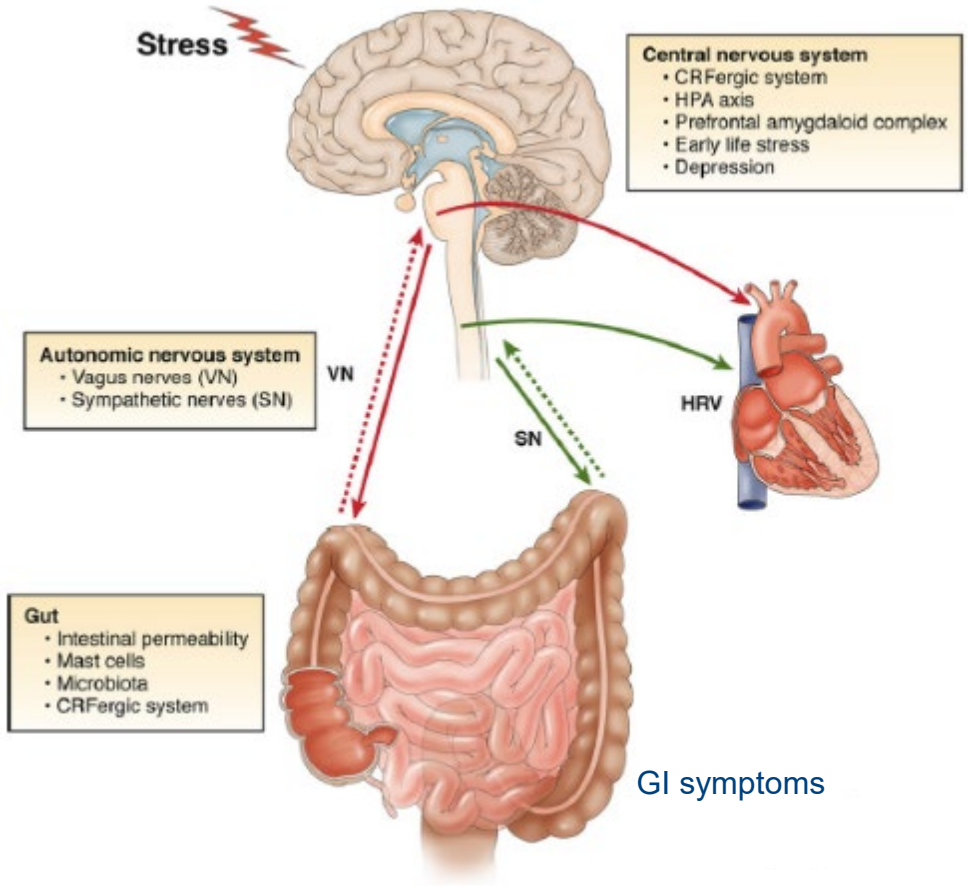
Drossman Gut 1999

Brain-Gut Axis

= bi-directionele beïnvloeding tussen
het maagdarmstelsel en de hersenen

Mediatoren: autonoom zenuwstelsel
HPA-as (CRF-ACTH-cortisol)





Bonaz et al. Gastroenterology 2013

Brain-Gut Axis

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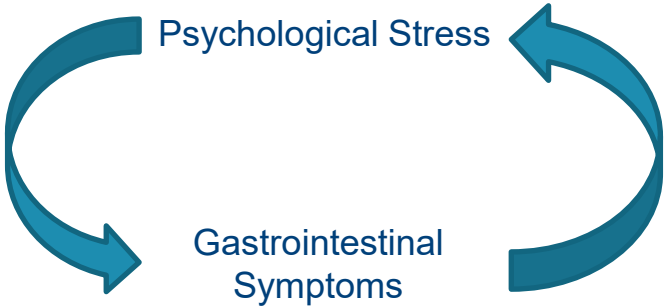

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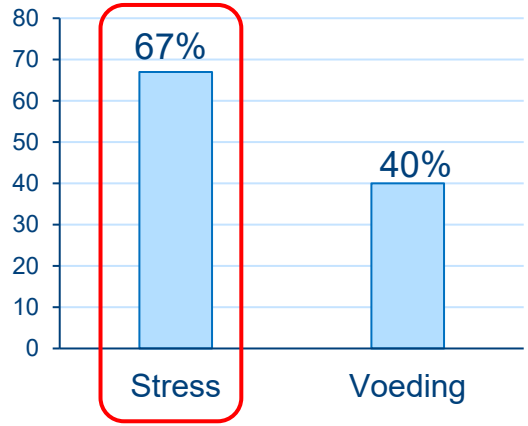
Uitlokkende factoren?



Van Den Houte et al. UEG Journal 2018

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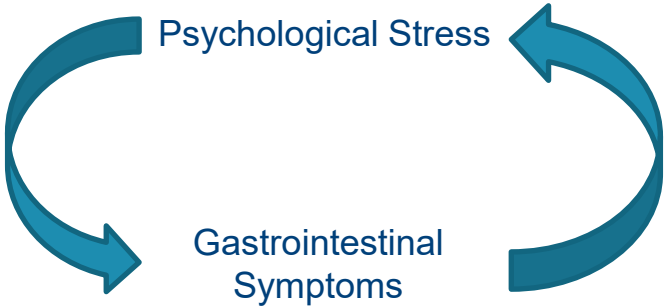
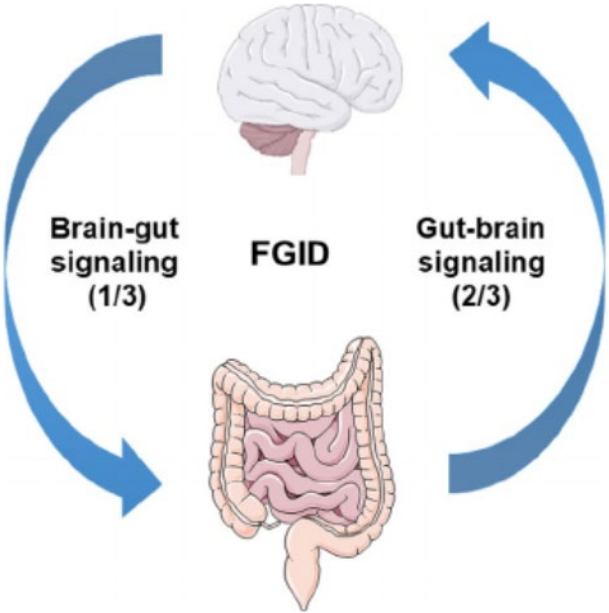
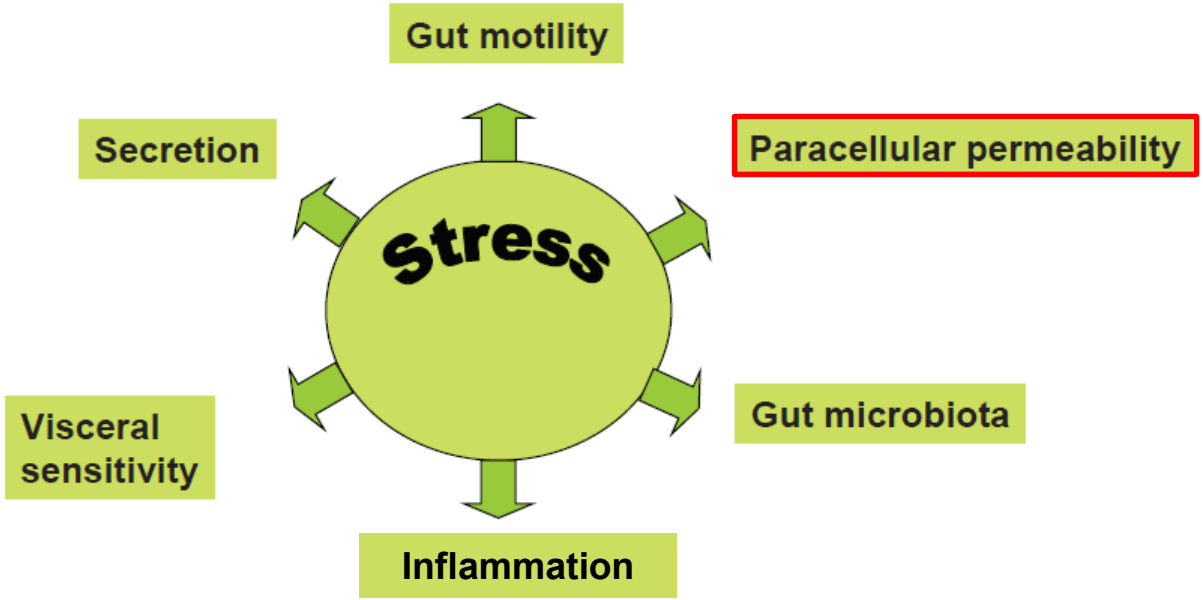


Prospectief bevolkingsonderzoek bij 1900 Australiërs.

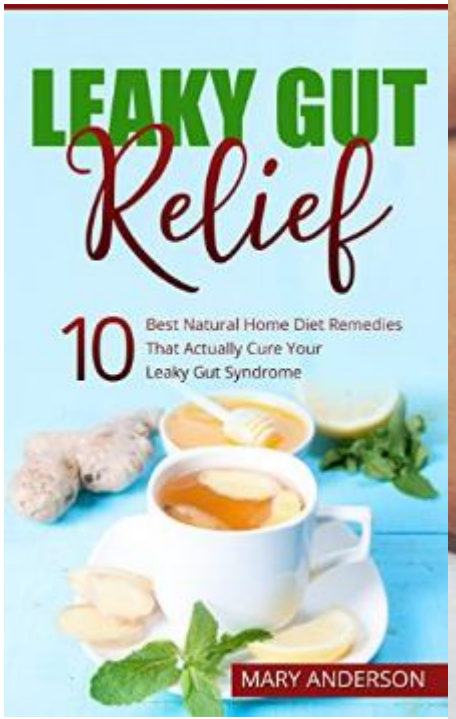


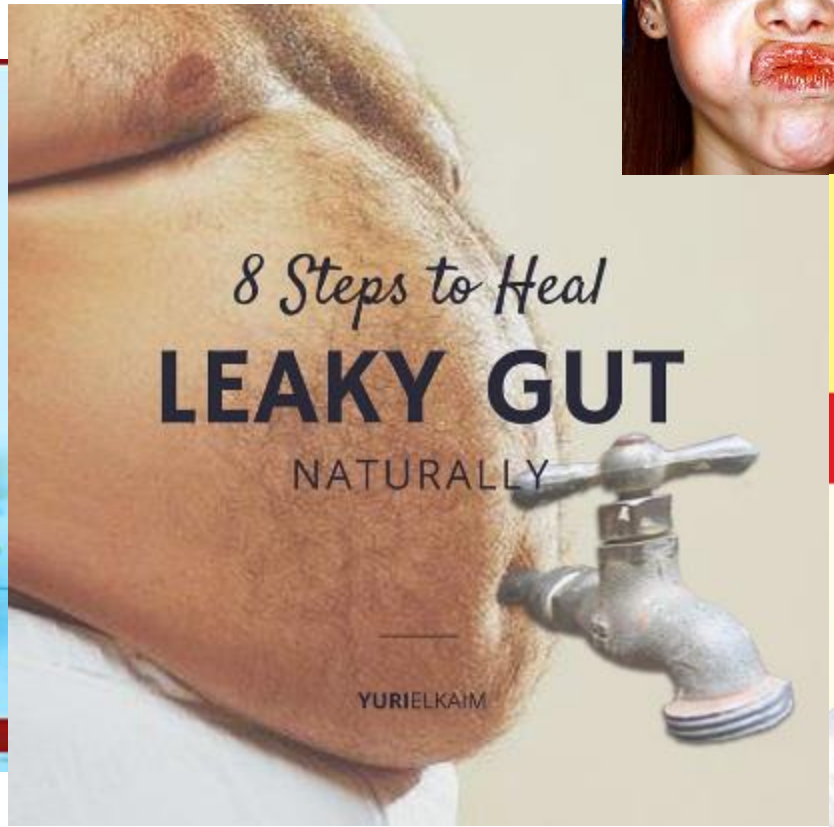
Wauters et al. Neurogastroenterol Motil 2021
Koloski et al. Aliment Pharmacol Ther 2016

Effect van stress op het maag-darmstelsel

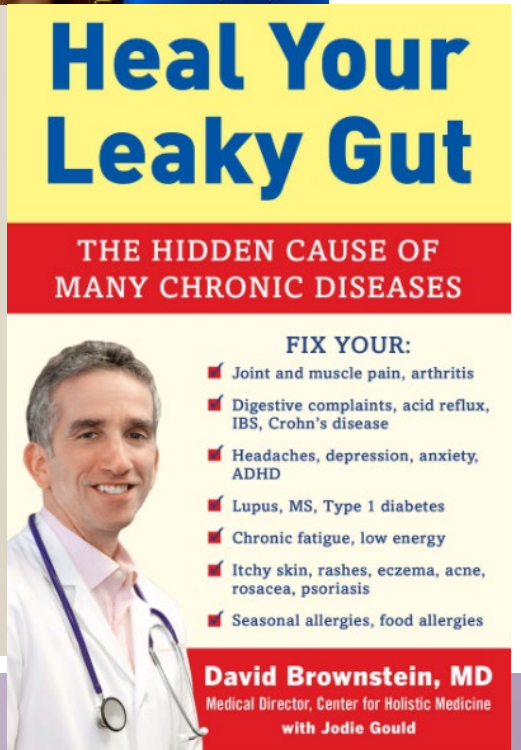


‘Leaky Gut’

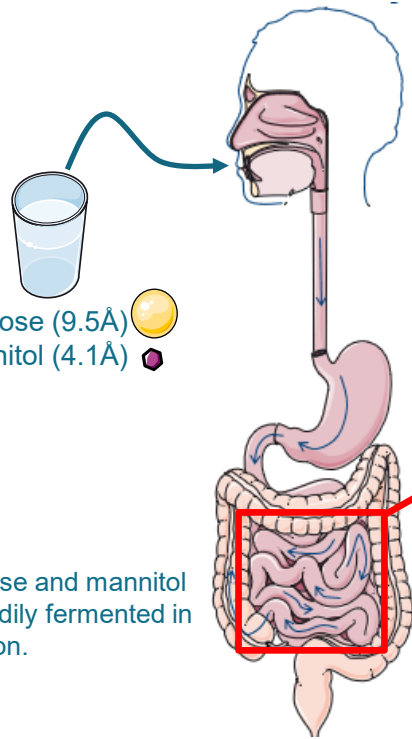

LEAKY GUT
Relief
10 Best Natural Home Diet Remedies That Actually Cure Your Leaky Gut Syndrome
MARY ANDERSON


8 Steps to Heal
LEAKY GUT
NATURALLY
YURIELKAIM


Do You Have
Leaky Gut
Syndrome?
SYMPTOMS:
Allergies
skin rashes
Anxiety
Poor concentration
Acne
Hives
NaturalHealthyConcepts.com

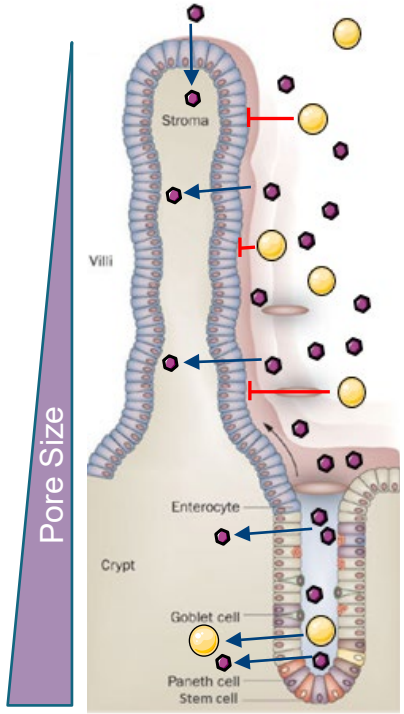

Heal Your
Leaky Gut
THE HIDDEN CAUSE OF
MANY CHRONIC DISEASES
FIX YOUR:
Joint and muscle pain, arthritis
Digestive complaints, acid reflux, IBS, Crohn's disease
Headaches, depression, anxiety, ADHD
Lupus, MS, Type 1 diabetes
Chronic fatigue, low energy
Itchy skin, rashes, eczema, acne, rosacea, psoriasis
Seasonal allergies, food allergies
David Brownstein, MD
Medical Director, Center for Holistic Medicine
with Jodie Gould

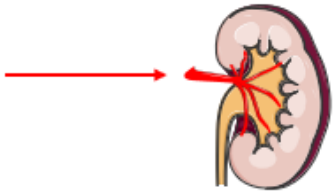
Intestinale Permeabiliteit

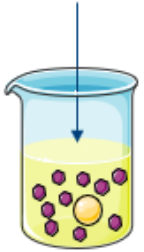


5g Lactulose (9.5Å)
2g Mannitol (4.1Å)

Lactulose and mannitol are readily fermented in the colon.







0-2h urine collection

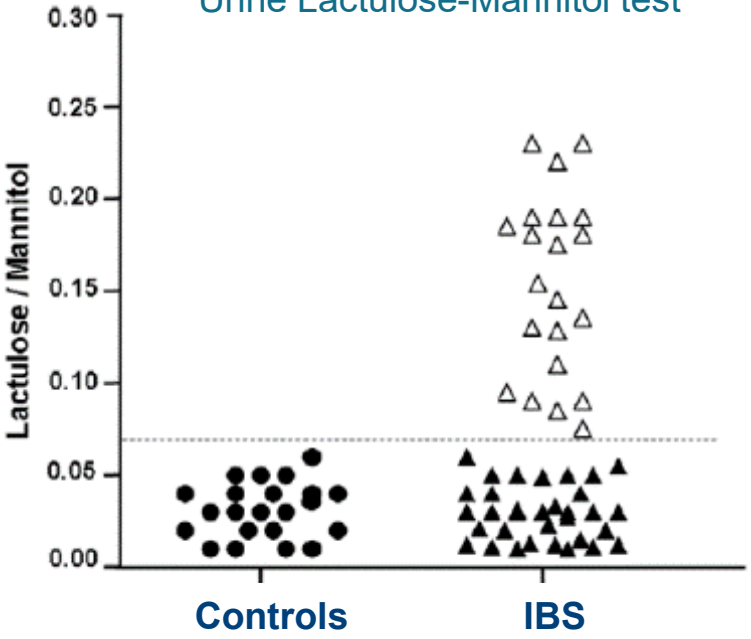
HPLC-ELSD



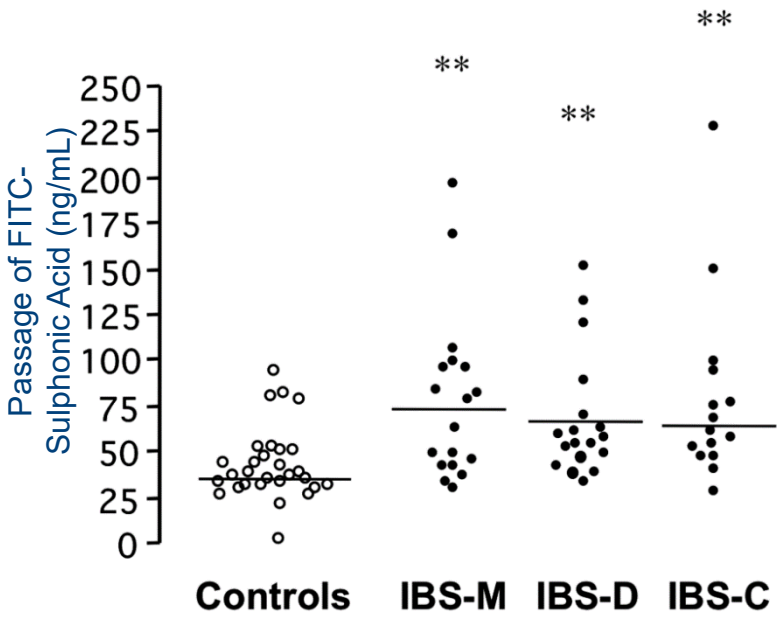
$$\frac{[\text{Lactulose}]}{[\text{Mannitol}]} \text{ (LMR)} \approx \text{Small Intestinal Permeability}$$

Permeabiliteit in IBS

Urine Lactulose-Mannitol test



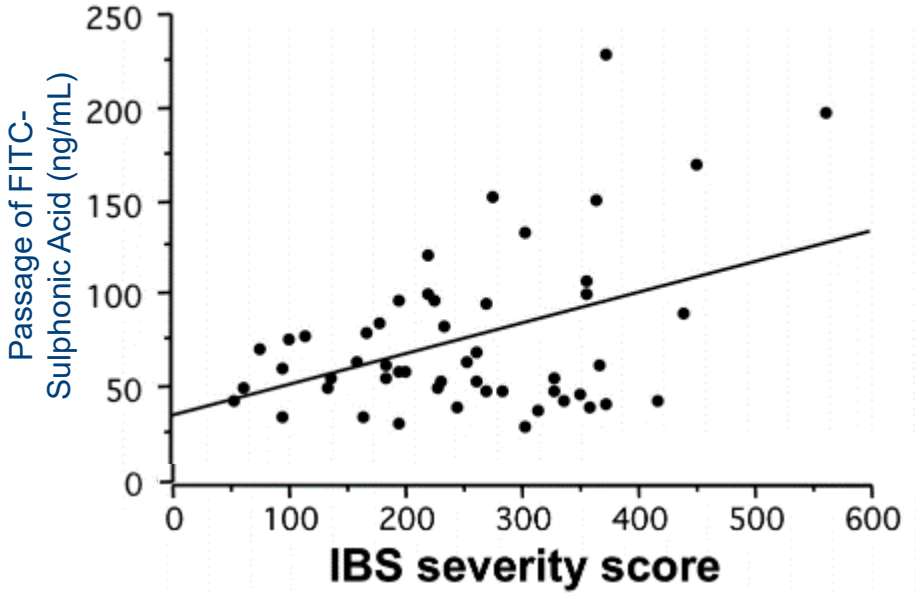
Cecal Biopsies in Ussing Chambers



Zhou et al. Pain 2009

Vivinus-Nebot et al. Gut 2013

Permeabiliteit in IBS



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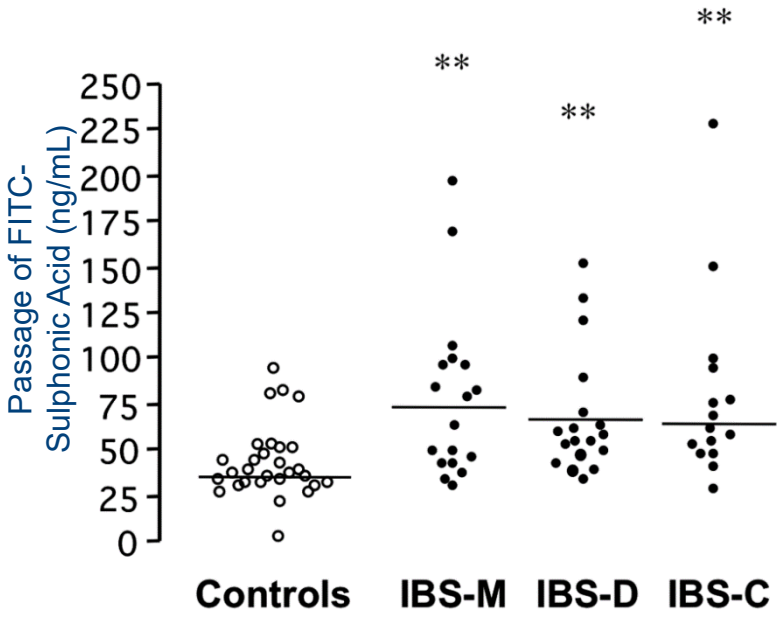


Vivinus-Nebot et al. Gut 2013

Permeabiliteit en Stress?

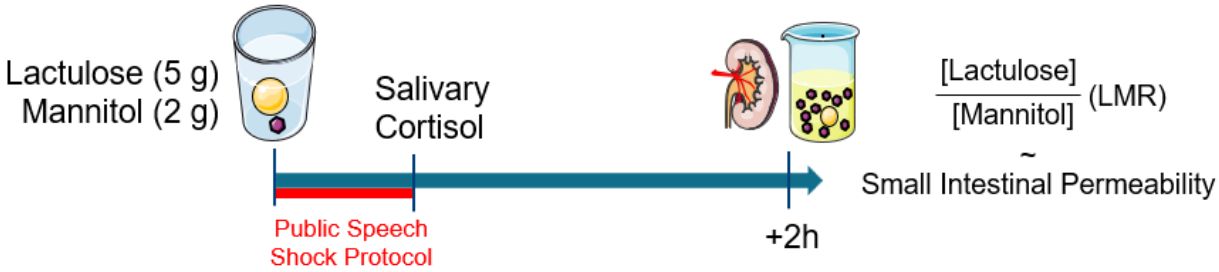
23 Healthy Undergraduate Students (12♂; 21±1.5ys)

Cross-over trial: **1/ Control**

2/ Public Speech
Oral exam in front of jury.

3/ Shock Protocol
20 countdown sequences over 30 min,
half of these followed by a painful electroshock.

4/ Indomethacin
NSAID, positive control (75mg -16h and 50mg -4h)



De test begint bij het verdwijnen van dit scherm en zal ongeveer 30 minuten duren.

Succes…

10

9

8

7

6

5

4

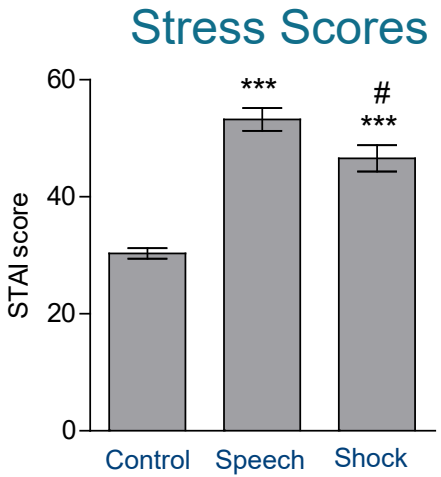
3

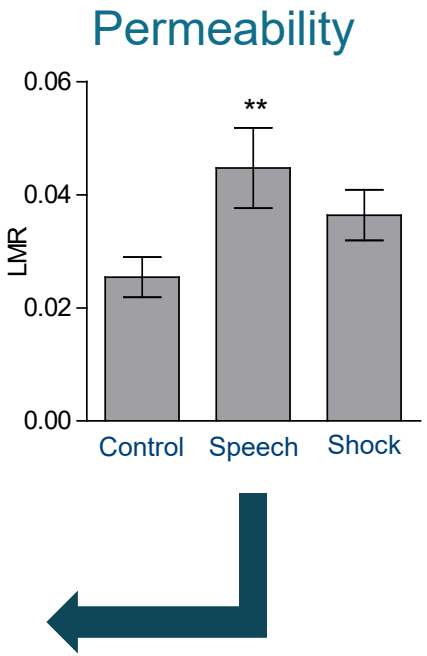
2

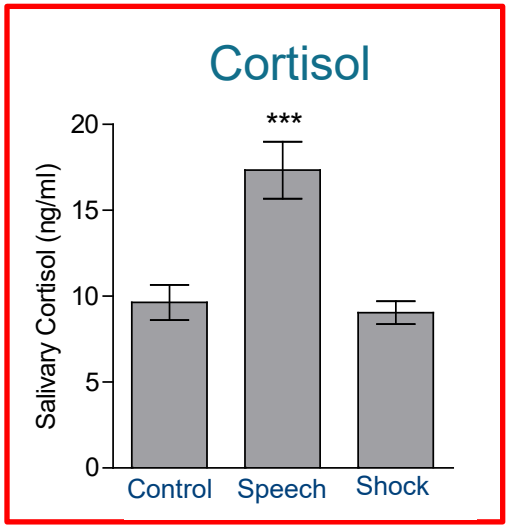
1

0

Permeabiliteit en Stress?



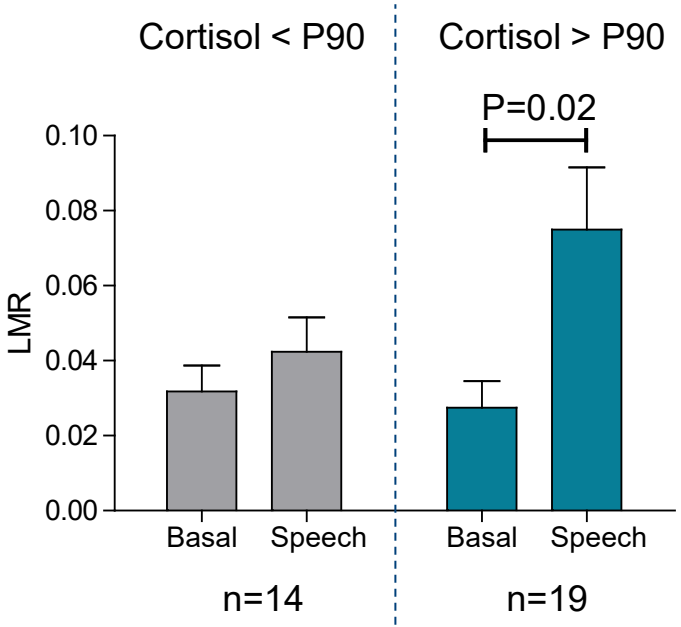




Psychologische stress verhoogt darmpermeabiliteit

Vanuytsel et al. Gut 2014

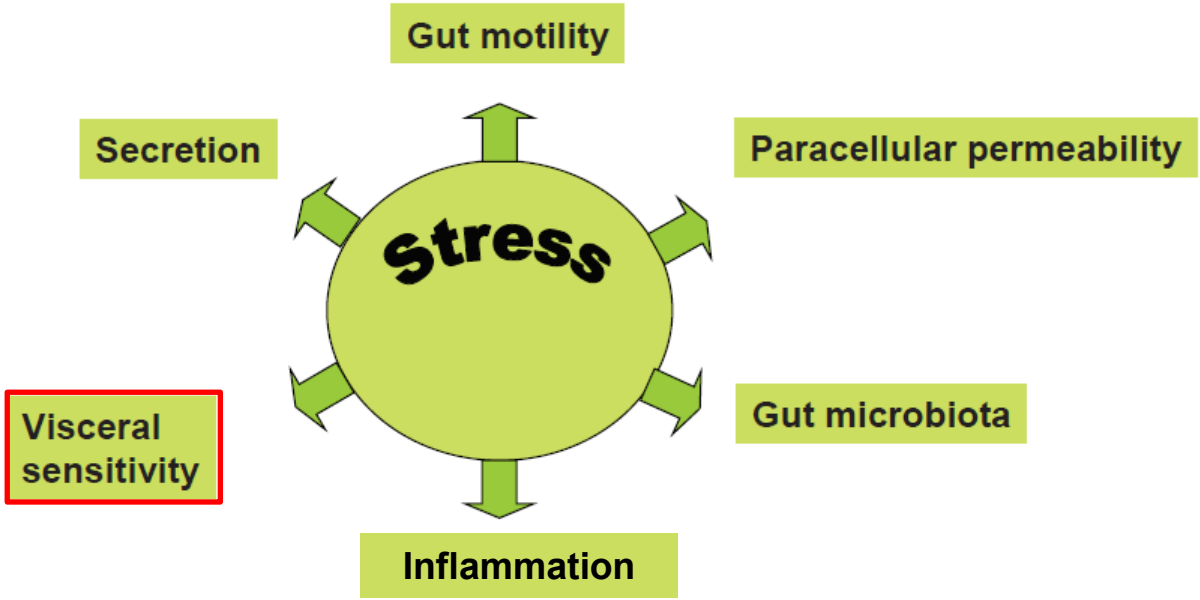
Permeabiliteit en Stress?



Psychologische stress verhoogt darmpermeabiliteit

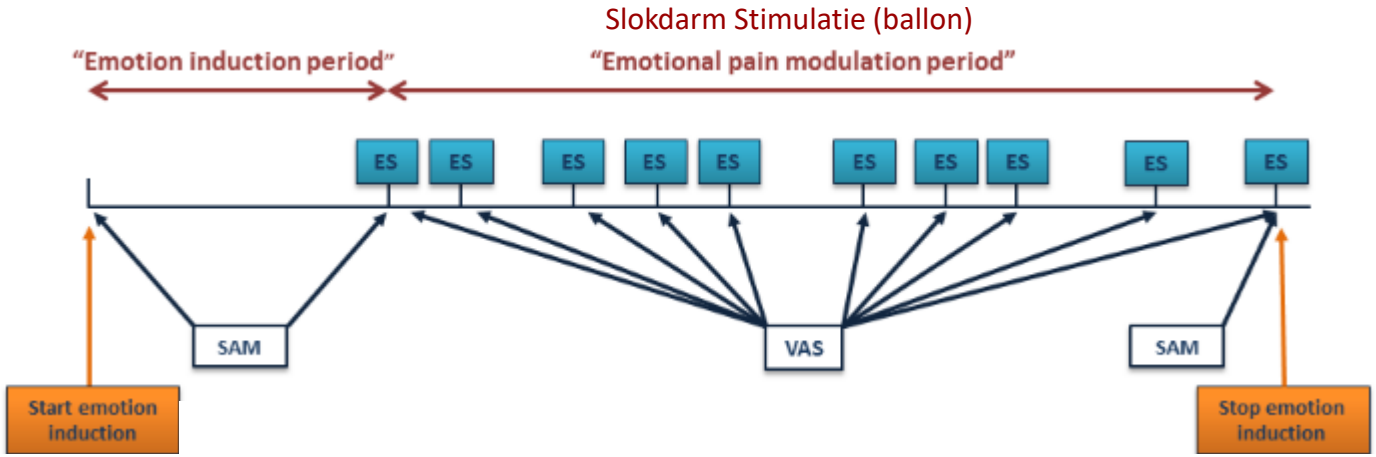
Vanuytsel et al. Gut 2014

Effect van stress op het maag-darmstelsel



Konturek et al. J Physiol Pharmacol 2011

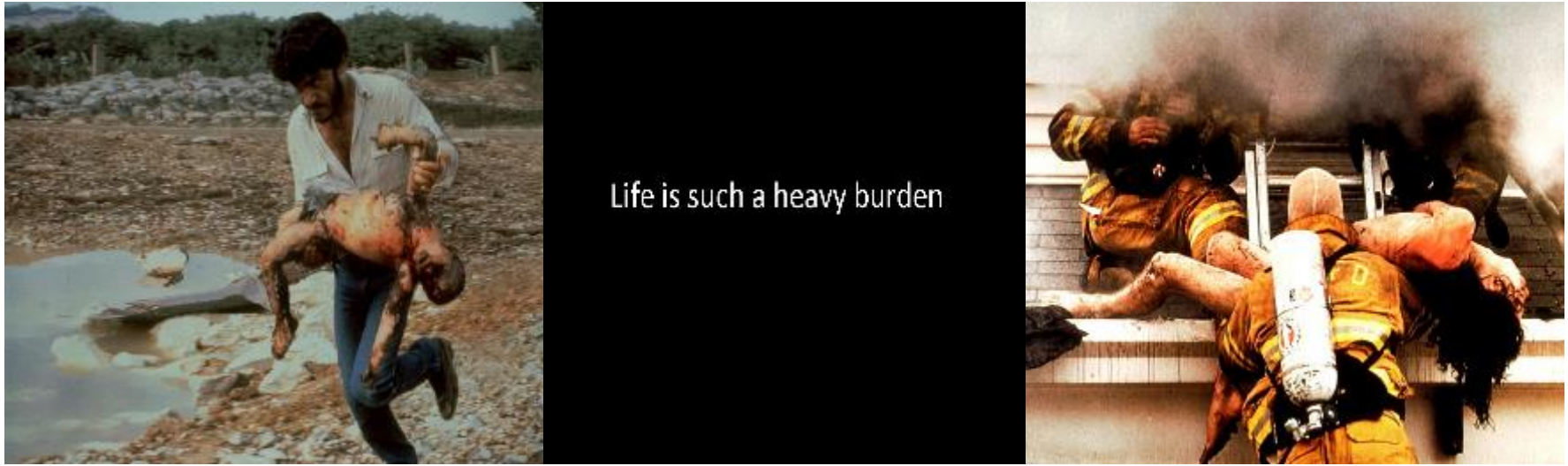
Emoties en GI gevoeligheid



Emotie inductie

- **Gevalideerde klassieke muziek**
- **Velten mood induction statements**
- **IAPS foto's**

Emoties en GI gevoeligheid



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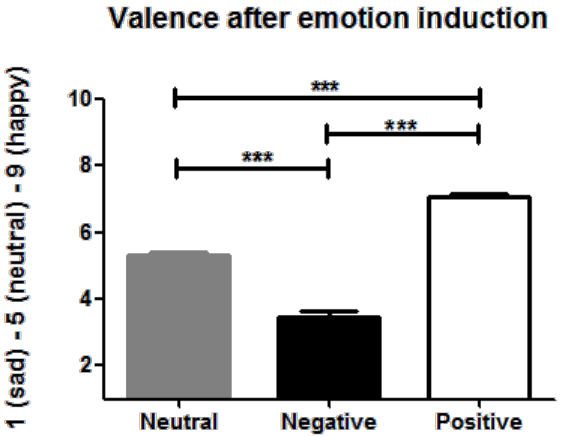
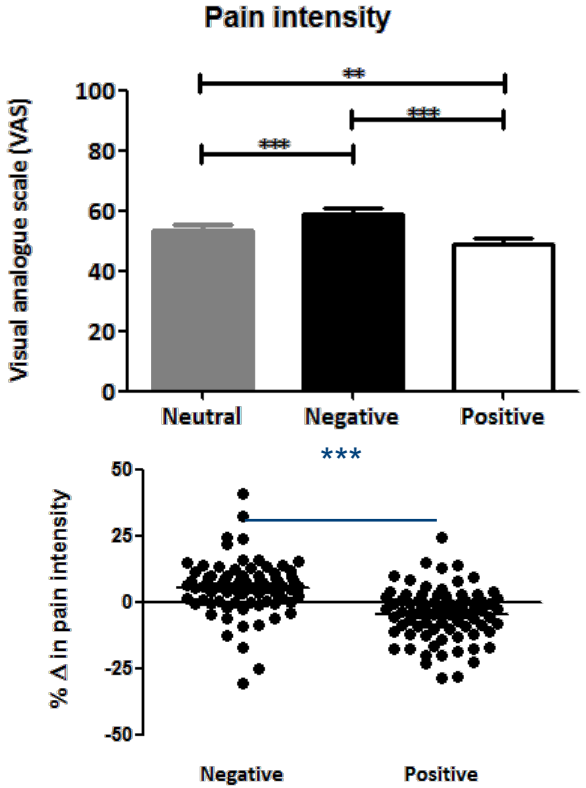
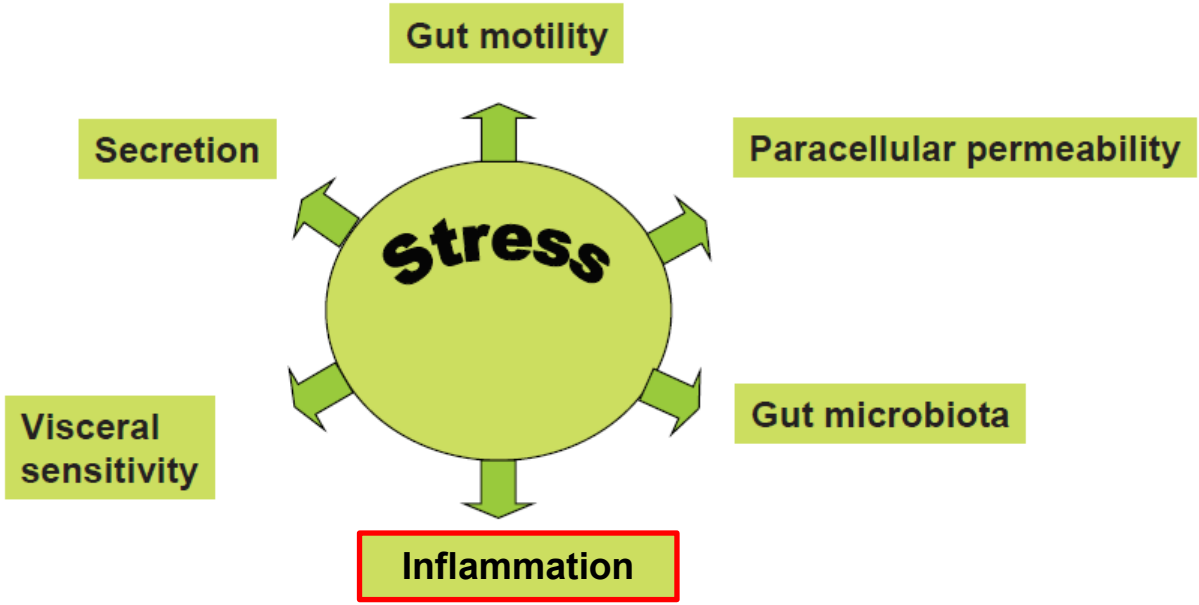




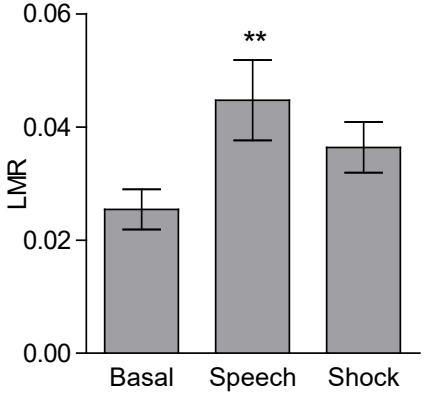
Negatieve emotie inductie zorgt voor toename van viscerale pijn.

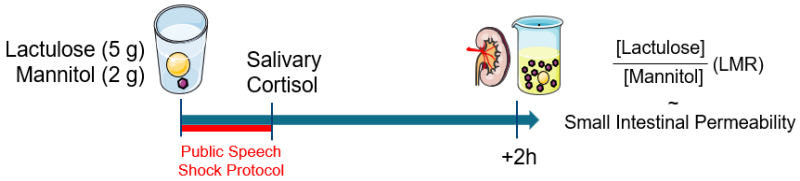
Effect van stress op het maag-darmstelsel



Stress en Mast Cellen

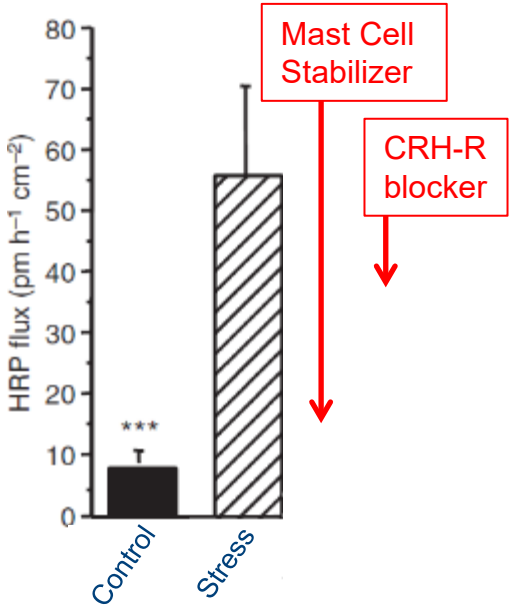
Permeability





Mediator?

Water Avoidance Stress in Rats



Vanuytsel et al. Gut 2014

Keita et al. Neurogastroenterol Motil 2010

Stress en Mast Cellen

13 Healthy Undergraduate Students (4♂; 22±1.4ys)

Cross-over trial:

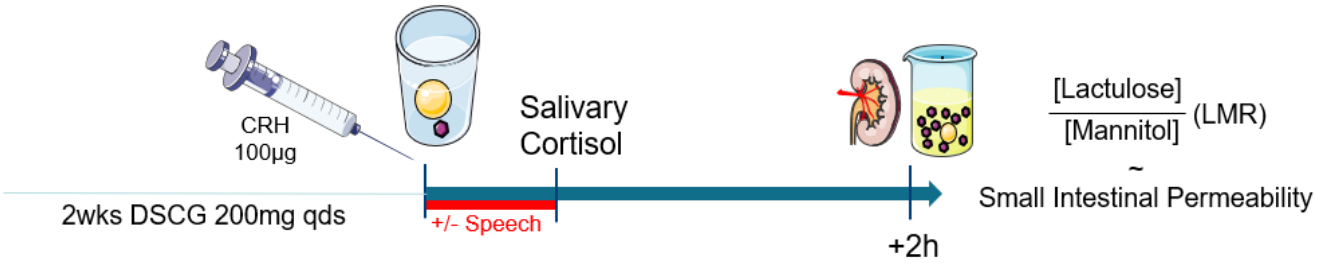
1/ Control

2/ Disodium Cromoglycate (DSCG, mast cell stabilizer) pretreatment
200 mg qds for 2 weeks per os

3/ Corticotropin-releasing hormone (CRH) treatment
intravenous bolus of 100µg CRH

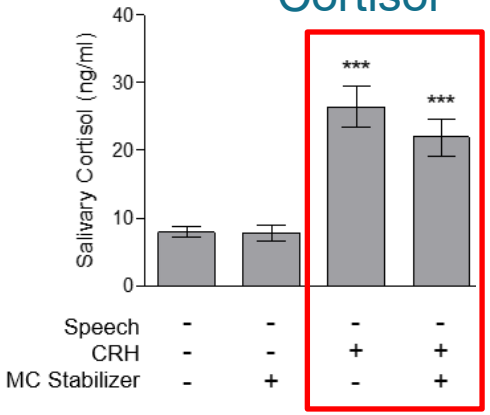
4/ CRH after DSCG pretreatment

5/ Public Speech after DSCG pretreatment

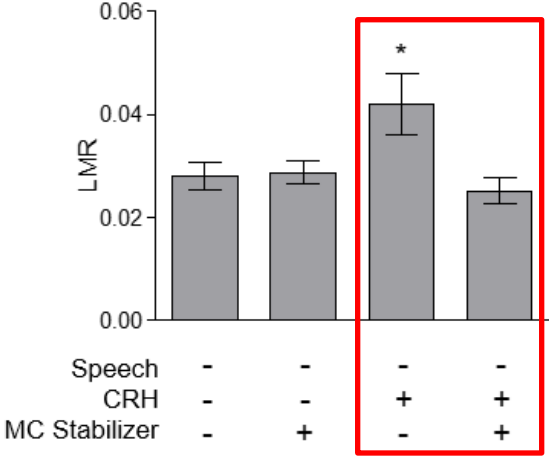


Stress en Mast Cellen

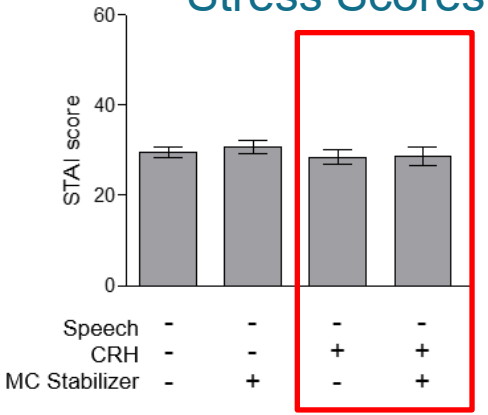
Cortisol



Permeability

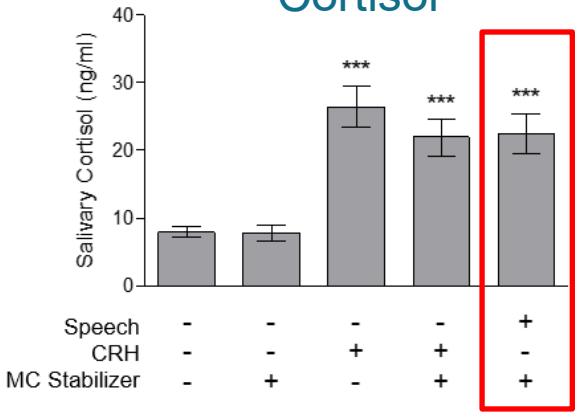


Stress Scores

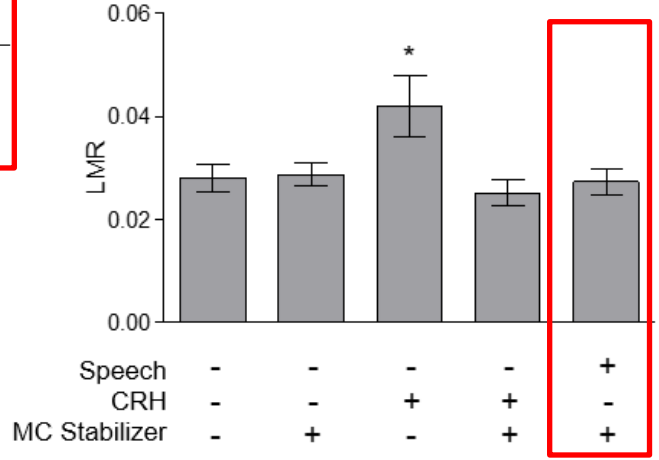


Stress en Mast Cellen

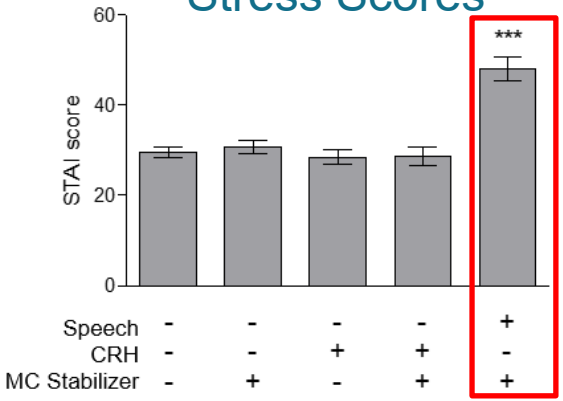
Cortisol



Permeability

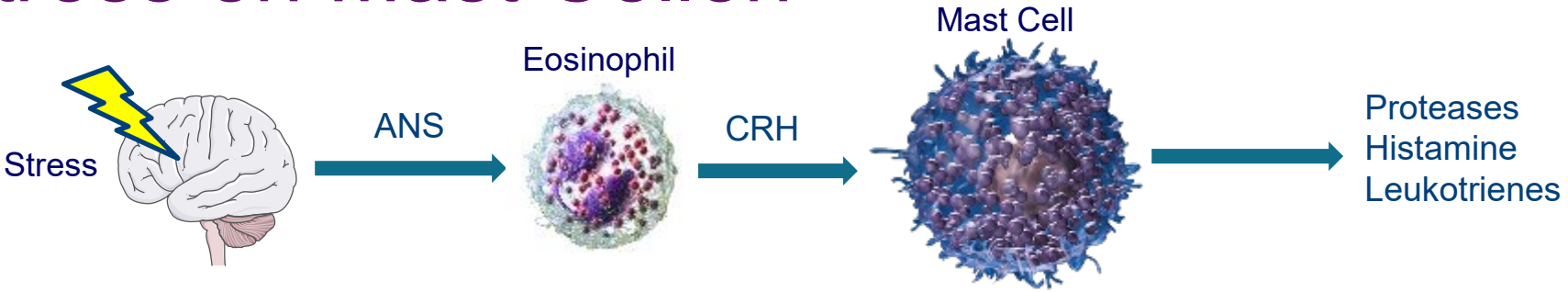


Stress Scores

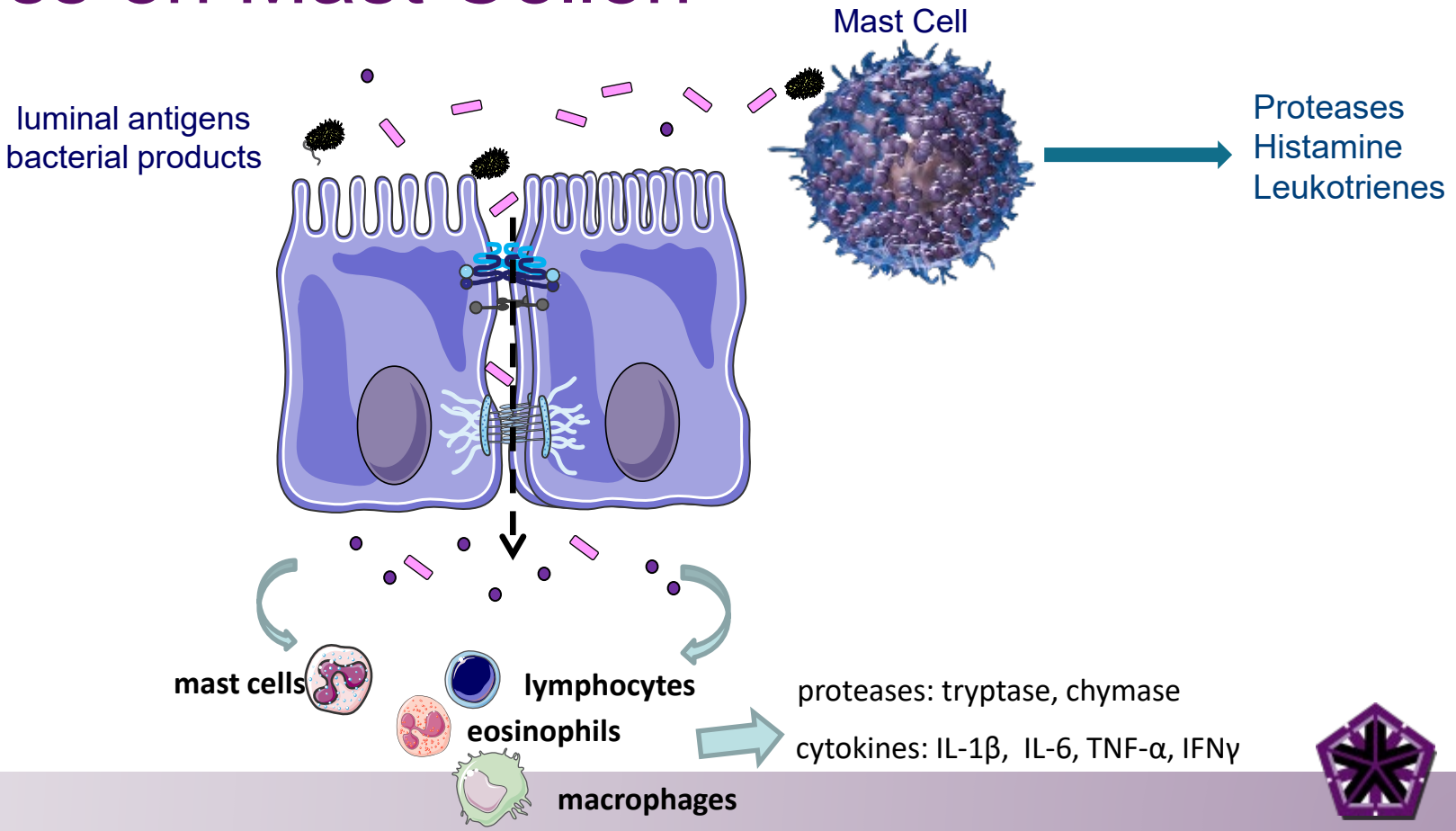


Vanuytsel et al. Gut 2014

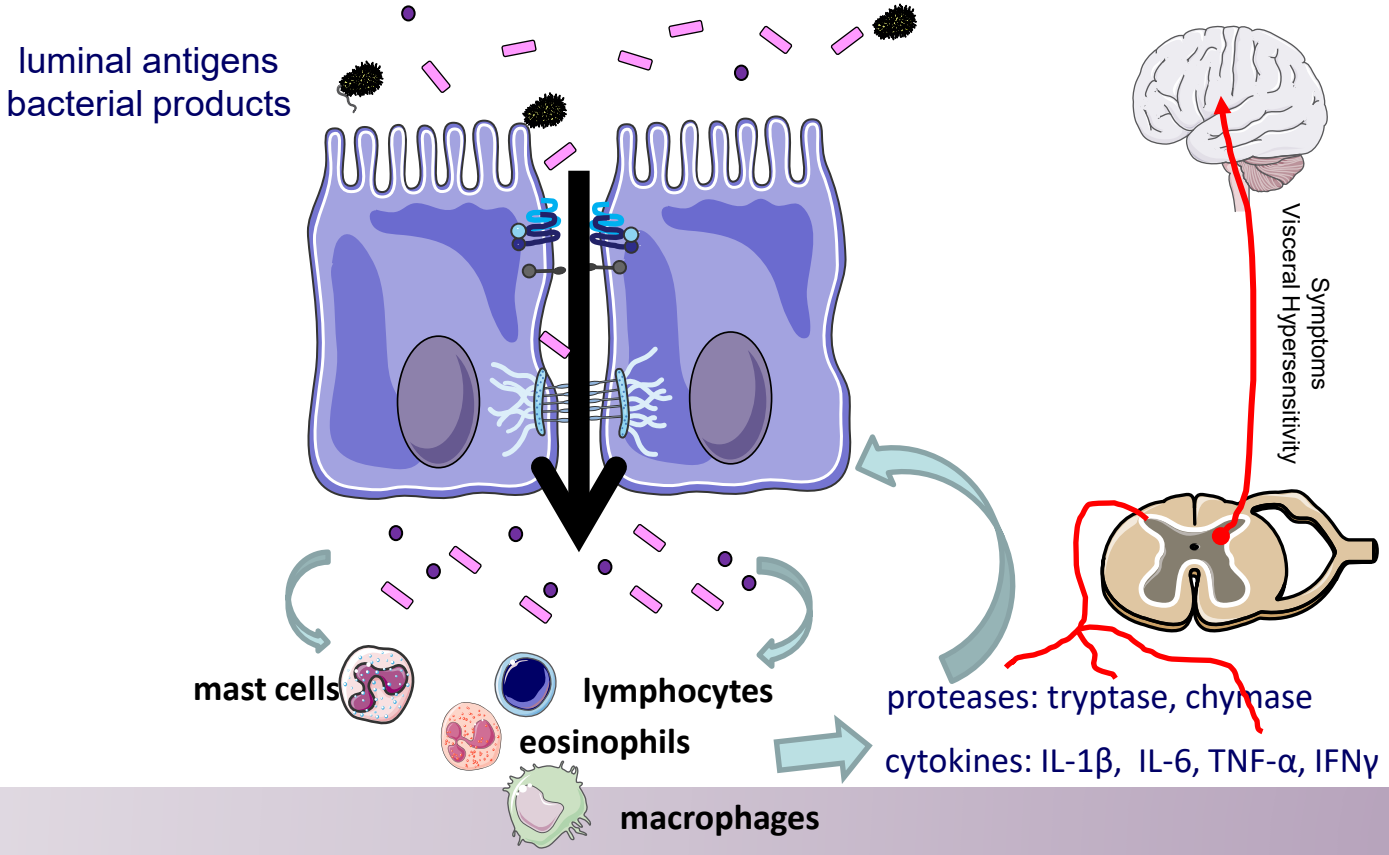
Stress en Mast Cellen



Stress en Mast Cellen



Stress en Mast Cellen

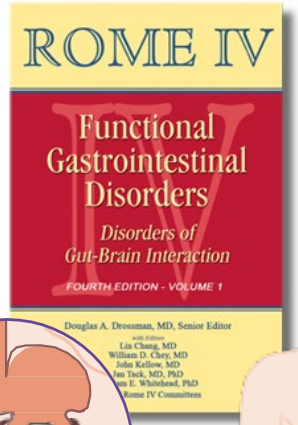


Stress en Eosinofielen

Functionele Dyspepsie

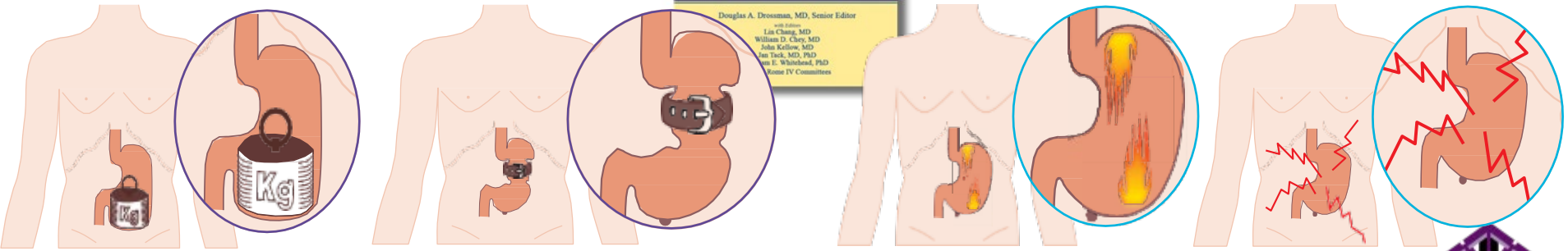
Postprandial distress syndrome (PDS)

Symptomen gerelateerd aan maaltijd (volheid, verzadiging)



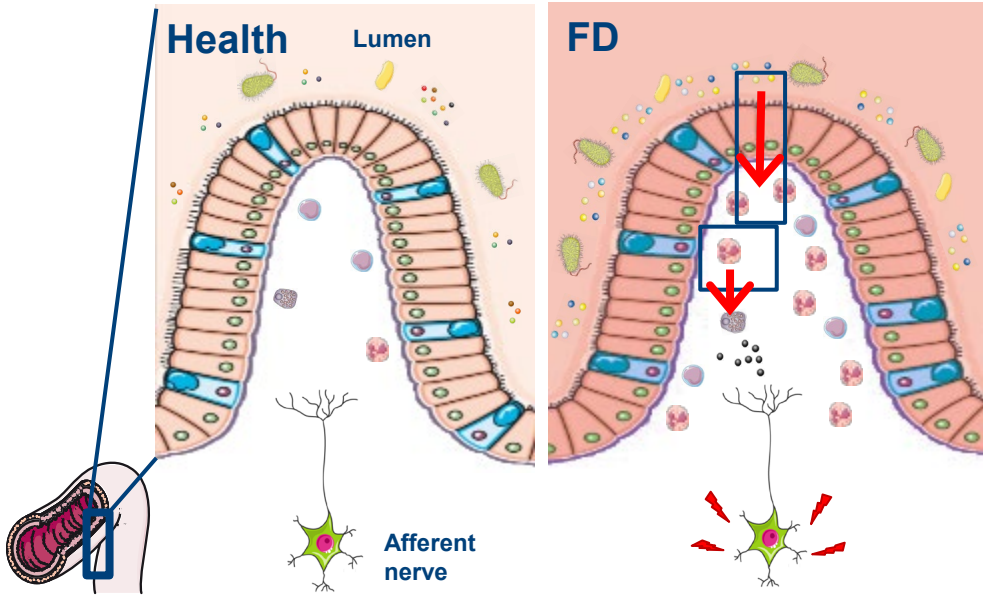
Epigastric pain syndrome (EPS)

Symptomen los van maaltijd (epigastrische pijn en branderigheid)



Stress en Eosinofielen

Sleutelrol van het **duodenum** bij pathofysiologie van functionele dyspepsie



Rol van psychologische factoren?

Duodenale permeabiliteit
Eosinofiel en Mast Cel infiltratie + activatie
Neuronale activatie

Wauters et al. Gut 2020

Stress en Eosinofielen

Duodenal eosinophilia and anxiety,
The Kalixanda 10-year follow-up study

EGD responders (73.4%) in 1999-2001
n=1000, mean age 54.0, 51.2% female

↓

Postal questionnaire responders (79.3%) in 2010
n=703, mean age 63.2, 51.9% female

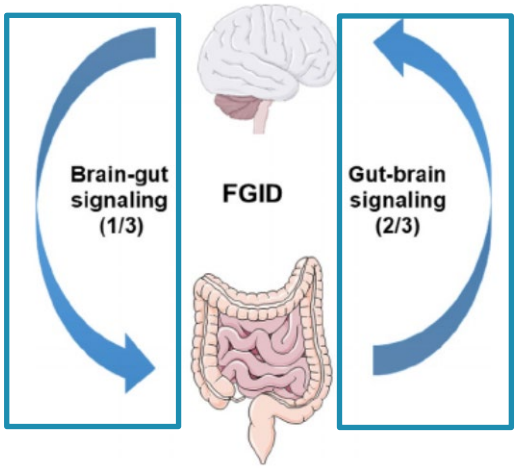
↓

Functional dyspepsia case control study
n=213, mean age 62.3, 66.2% female

Sterk verband tussen eosinofielen en angst (OR 11.7)

Verhoogde angst bij start: 7x hoger kans op FD na 10j

Verhoogde eosinofielen bij start: 4.5x hogere kans op toegenomen angst na 10 jaar



Ronkainen et al. Neurogastroenterol Motil 2021
Wauters et al. Neurogastroenterol Motil 2021

Impact op behandeling

Non-pharmacological therapy with central mechanism:

- Patient-physician relationship
- Education
- Cognitive Behavioral Therapy (CBT)
- Hypnotherapy

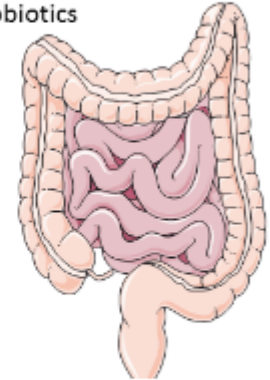


Pharmacological therapy with central mechanism:

- Tricyclic Antidepressants (TCA)
- Selective Serotonin Reuptake Inhibitors (SSRI)

Non-pharmacological therapy with peripheral mechanism:

- Low FODMAP diet
- Fiber supplements (psyllium)
- Probiotics



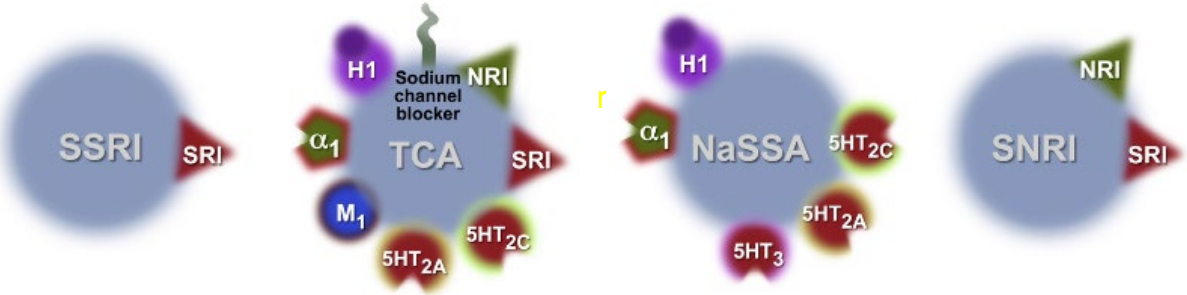
Pharmacological therapy with peripheral mechanism:

- Antispasmodics / Peppermint Oil
- Antibiotics: Rifaximin
- 5HT3-antagonists: Alosetron (IBS-D)
- Lubiprostone (IBS-C)
- Linaclotide (IBS-C)

Behandeling: neuromodulatoren

Gut-brain modulators for functional GI disorders

SSRIs	TCAs	Tetracyclic antidepressant	SNRIs
(paroxetine, fluoxetine, sertraline, citalopram, escitalopram)	(amitriptyline, nortriptyline, imipramine, desipramine)	(mirtazapine, mianserin, trazodone)	(duloxetine,venlafaxine, desvenlafaxin, milnacipran)
When anxiety, depression, and phobic features are prominent with FGIDs	**First-line treatment** when pain is dominant in FGIDs	Treatment of early satiety nausea/vomiting, weight loss and disturbed sleep	Treatment when pain is dominant in FGIDs or when side effects from TCAs preclude treatment



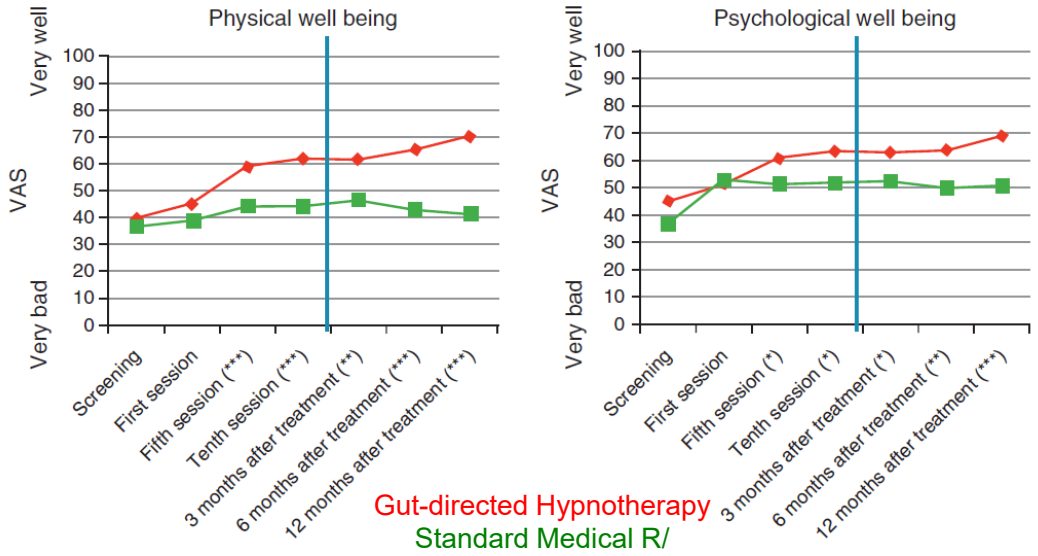
Behandeling: neuromodulatoren

- Psychiatric co-morbidity (anxiety, depression)
- Non-specific effects on general well-being, sleep quality
- Effects on pain-related brain circuits
  (emotional and cognitive modulation included)
- Effects on pain transmission in the dorsal horn by descending projections from brainstem nuclei
- Impact on neuroplasticity: regrowth of neurons in pain-modulating areas
  (e.g. anterior cingulate cortex)
- Effects on peripheral GI physiology:
  TCA slow colonic transit - SSRI accelerate transit



Hypnotherapie

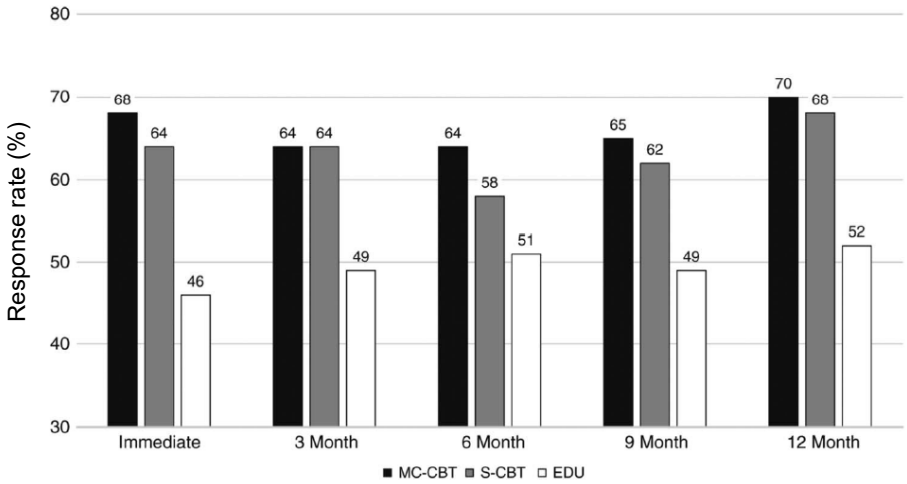
- 100 patiënten met IBS (Rome III) niet beantwoordend aan standaard therapie
- 10x45min sessies hypnotherapie (6 pts/groep) gedurende 12 wk+ standaard medische behandeling vs. standaard medische behandeling

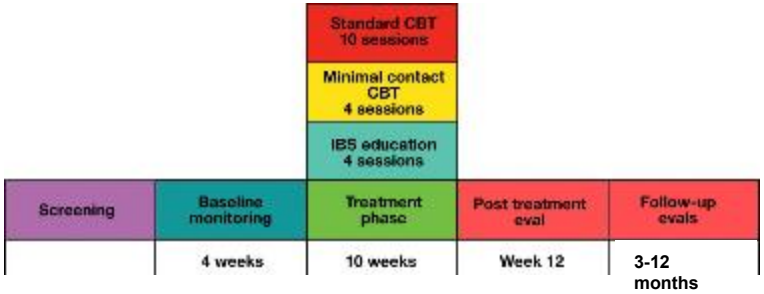


Moser et al. Am J Gastroenterol 2013

Cognitieve Gedragstherapie (CBT)

436 IBS (Rome III) patiënten
CBT (minimal contact vs. standaard) vs. educatie







Lackner et al. Gastroenterology 2018

Conclusies

- Stress en psychologische comorbiditeit zijn frequent binnen functionele gastro-intestinale aandoeningen
- Complexe en bidirectionele relatie
- Groeiend inzicht in onderliggende mechnismen: permeabiliteit, mechanismen
- Therapieën gericht op centraal zenuwstelsel zijn effectief binnen functionele gastro-intestinale aandoeningen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