The role of the microbiome and the gut-brain axis in health and disease and potential therapeutic approaches

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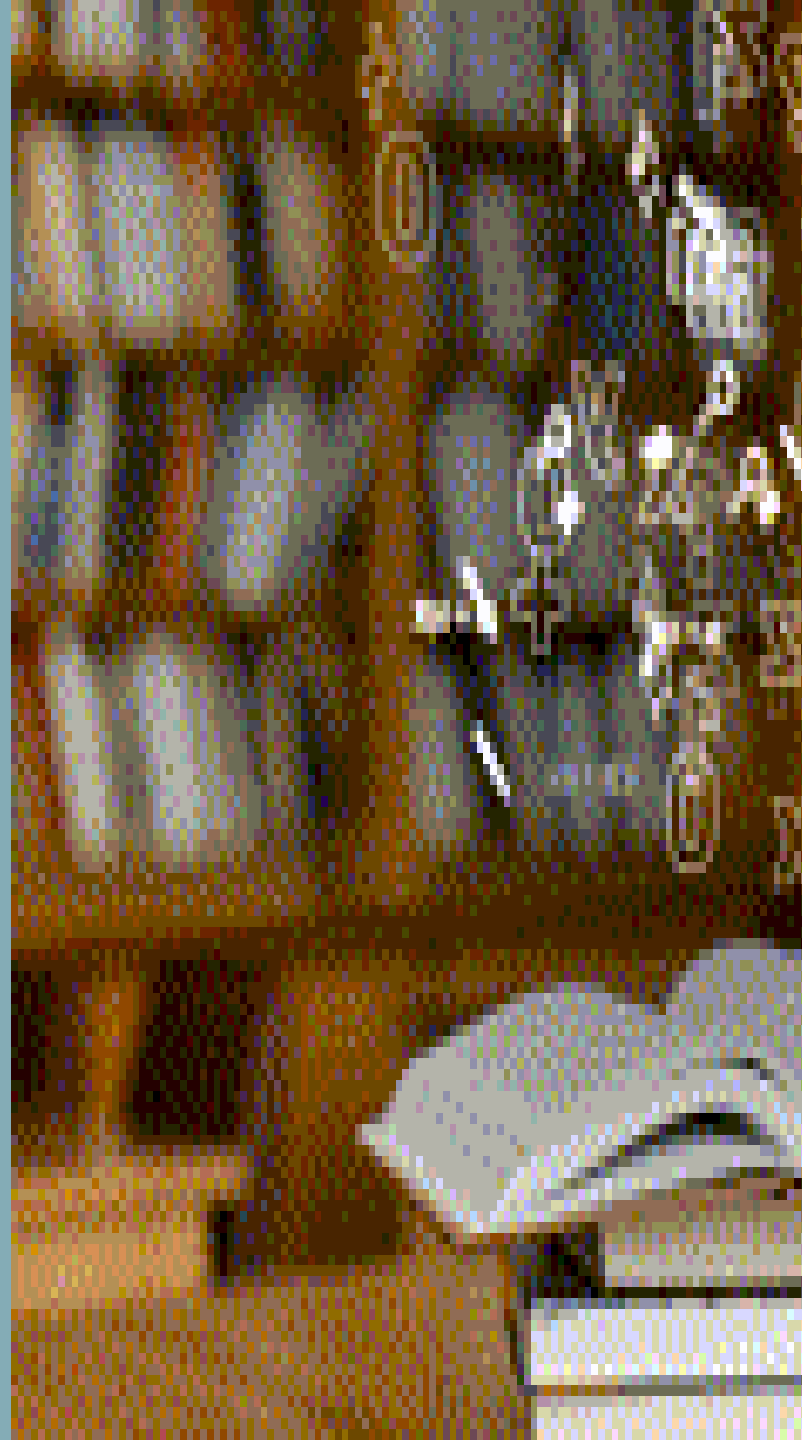
LEARNING OBJECTIVES

1.Overview of the current research on the gut-brain axis with a focus on neurological conditions

2. Be aware of gut-brain interactions and their communication pathways

3. Understand how healthy gut function (Eubiosis) and unhealthy gut function (Dysbiosis) contribute to health and ill health

4. Be aware of evidence-based interventions to promote Eubiosis



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THE GUT-BRAIN AXIS GBA

- The gut brain-axis is a biological pathway first detected in the 1960's when it came to light that the same neuropeptides were present in gut and brain (Pearse, 1969).

- It is a bi-directional signalling systems (endocrine, immune, autonomic, enteric and as well as the hypothalamic pituitary adrenal (HPA) axis) and microbiome metabolites and products
- comprises a physical route, via the vagal nerves, connecting brain-gut-brain
- The enteric nervous system (ENS) is located in the gastrointestinal tract. It is a system of sensory neurons, motor neurons, and interneurons that extends throughout the tract and forms part of the ANS

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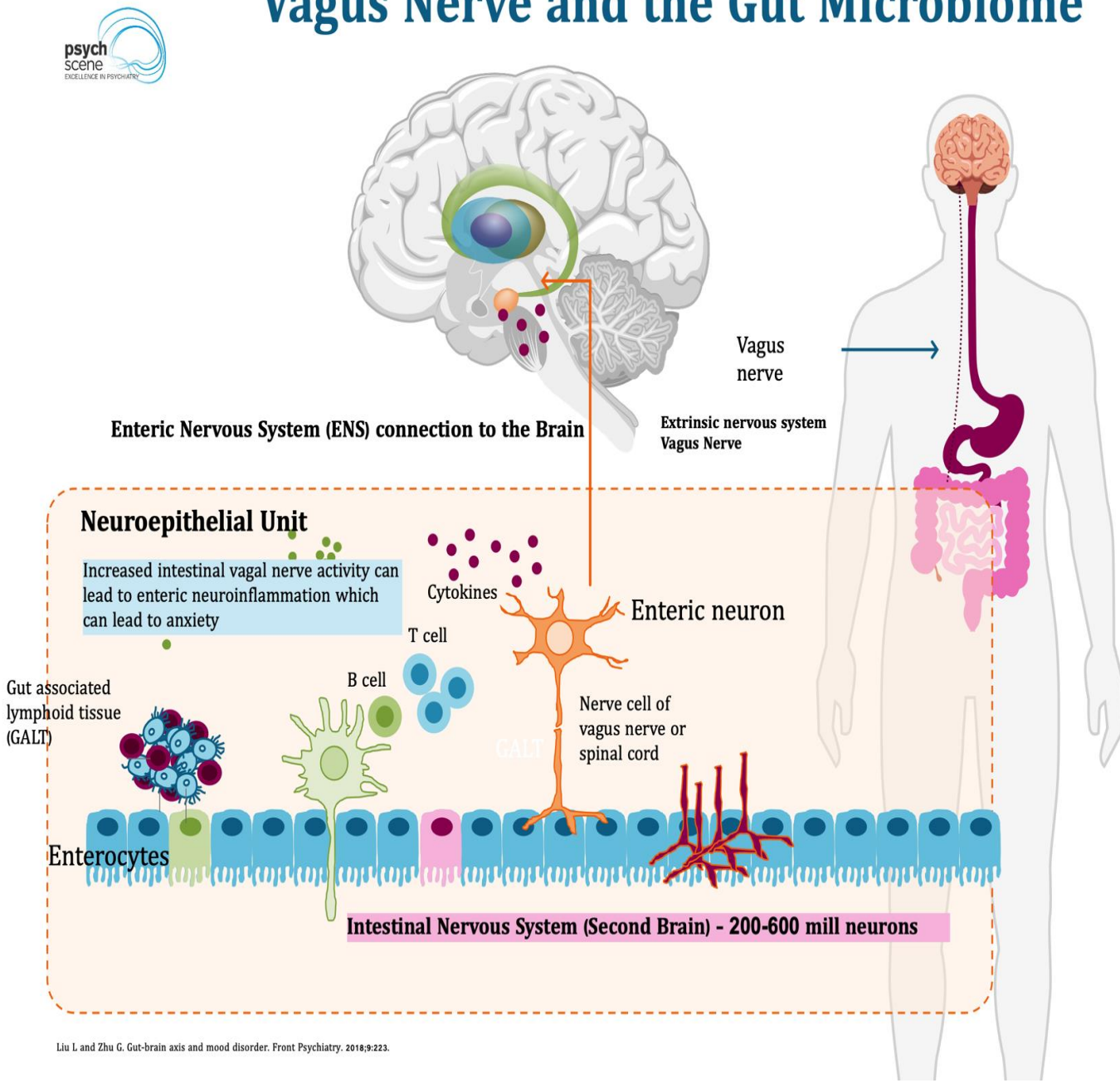
- The GBA implicated in many conditions, IBS, diabetes, obesity, developmental and psychological disorders, dementia and neurological conditions

- In recent years, the study of gut microbiota has become one of the most important areas in biomedical research

- So much so that the term is now microbiota-gut-brain axis (Rhee et al., 2009; Collins et al.2012)



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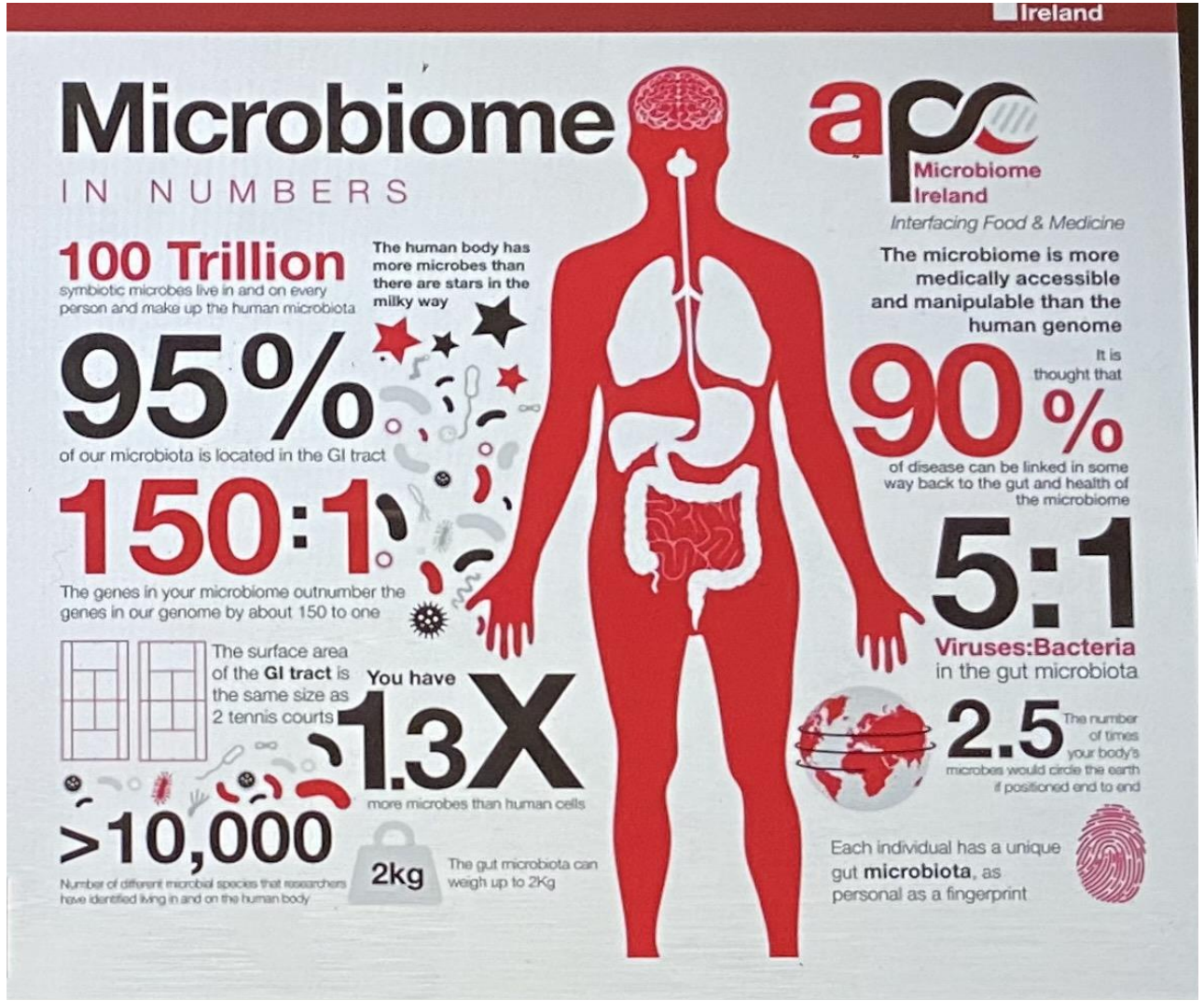
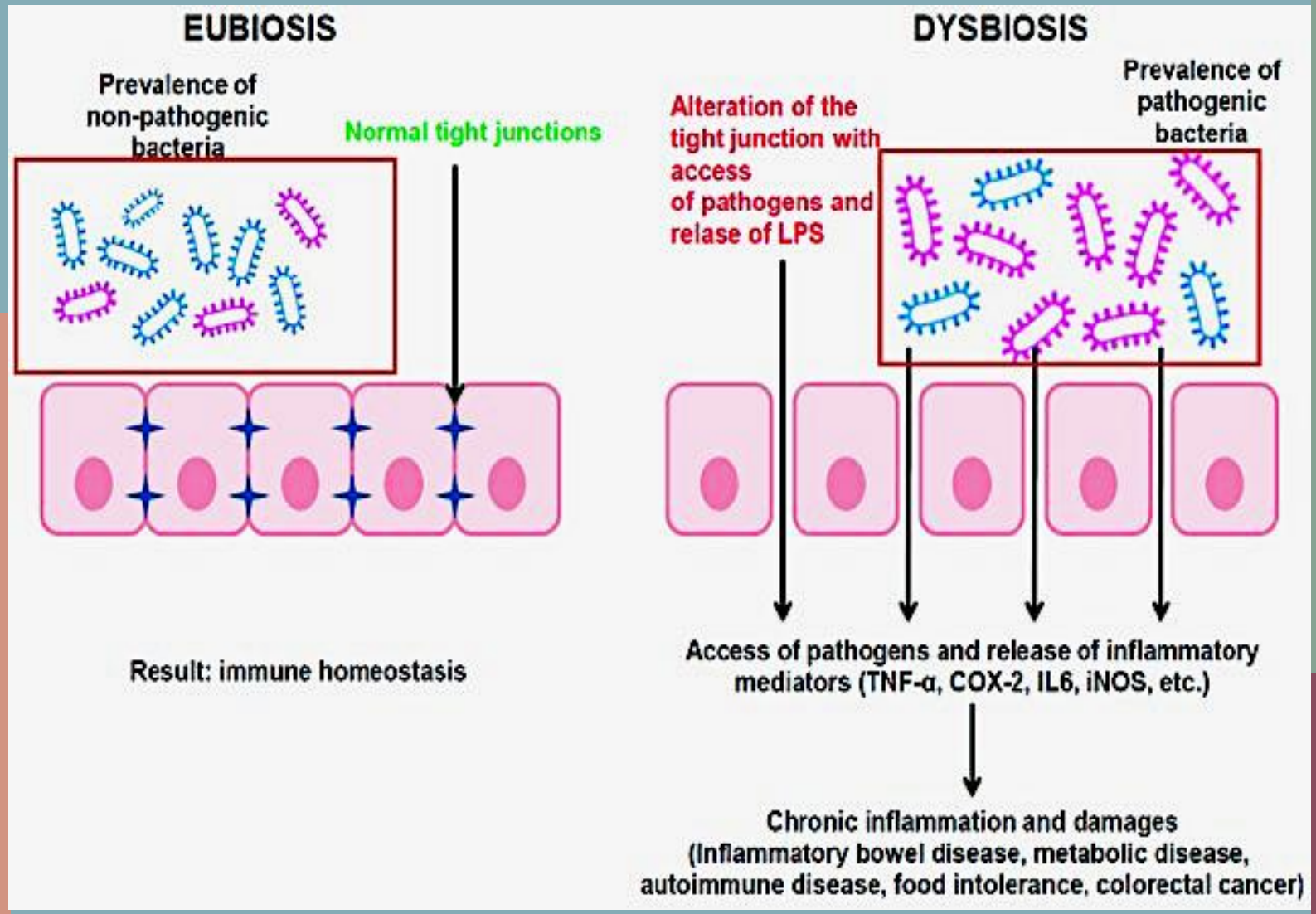
Microbiome -Gut-Brain



- Gut filled with microbes, virus, fungi and archaea
- There are 14,000 viruses
- Each have unique MB but there are also *signatures*
- Microbes and their metabolites in constant communication with host cells and brain

The delicate equilibrium between eubiosis and dysbiosis in the bowels. Eubiosis is the condition in which saprophytic bacteria are present in the mucus-microbiotic layer of the bowel (either the small or the large one). Dysbiosis is a condition in which pathogenic bacteria (Pathogenic bacteria are represented with purple frame, non-pathogenic have a blue frame) predominate and cause changes in the intercellular tight junctions leading to tissue damage.



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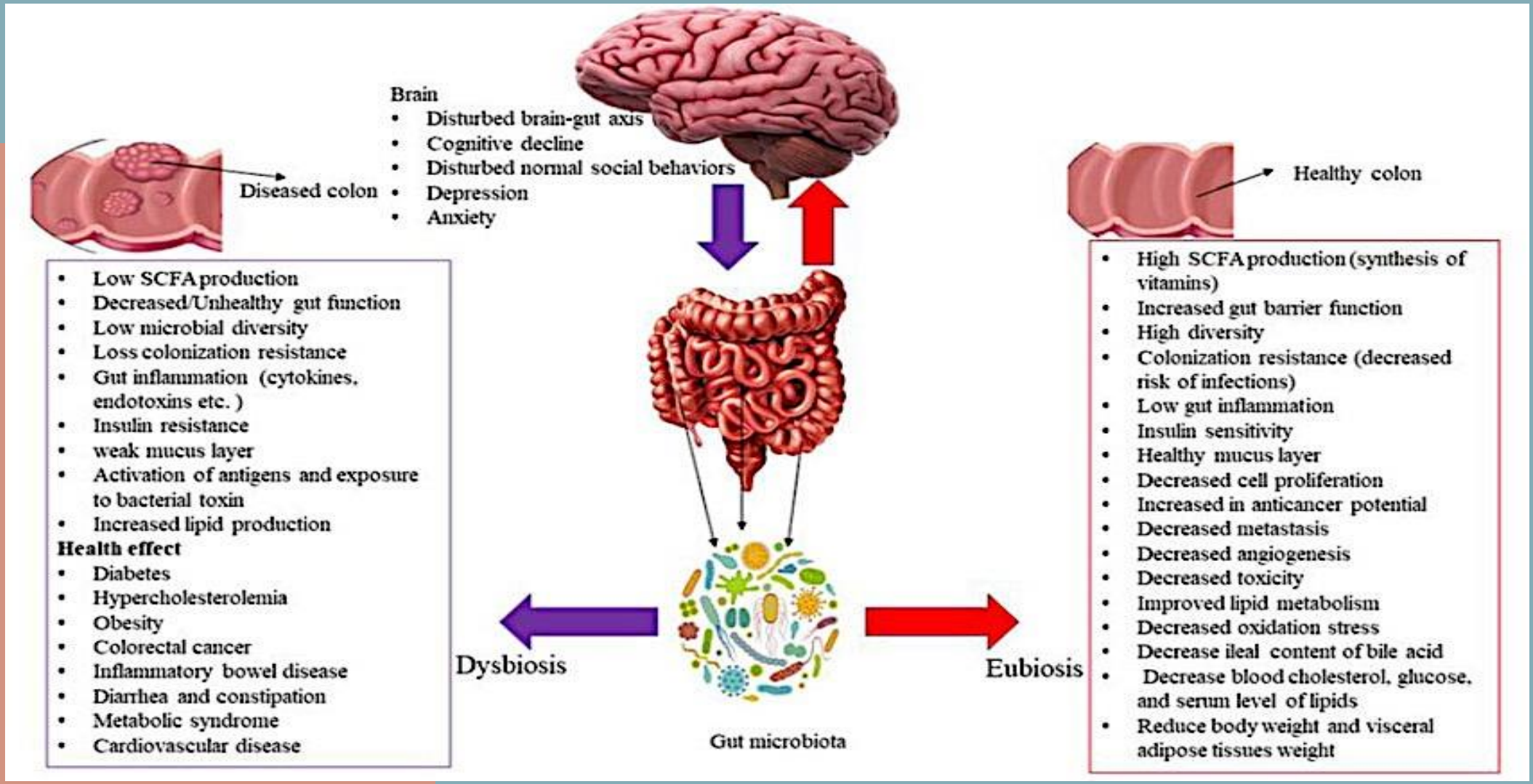
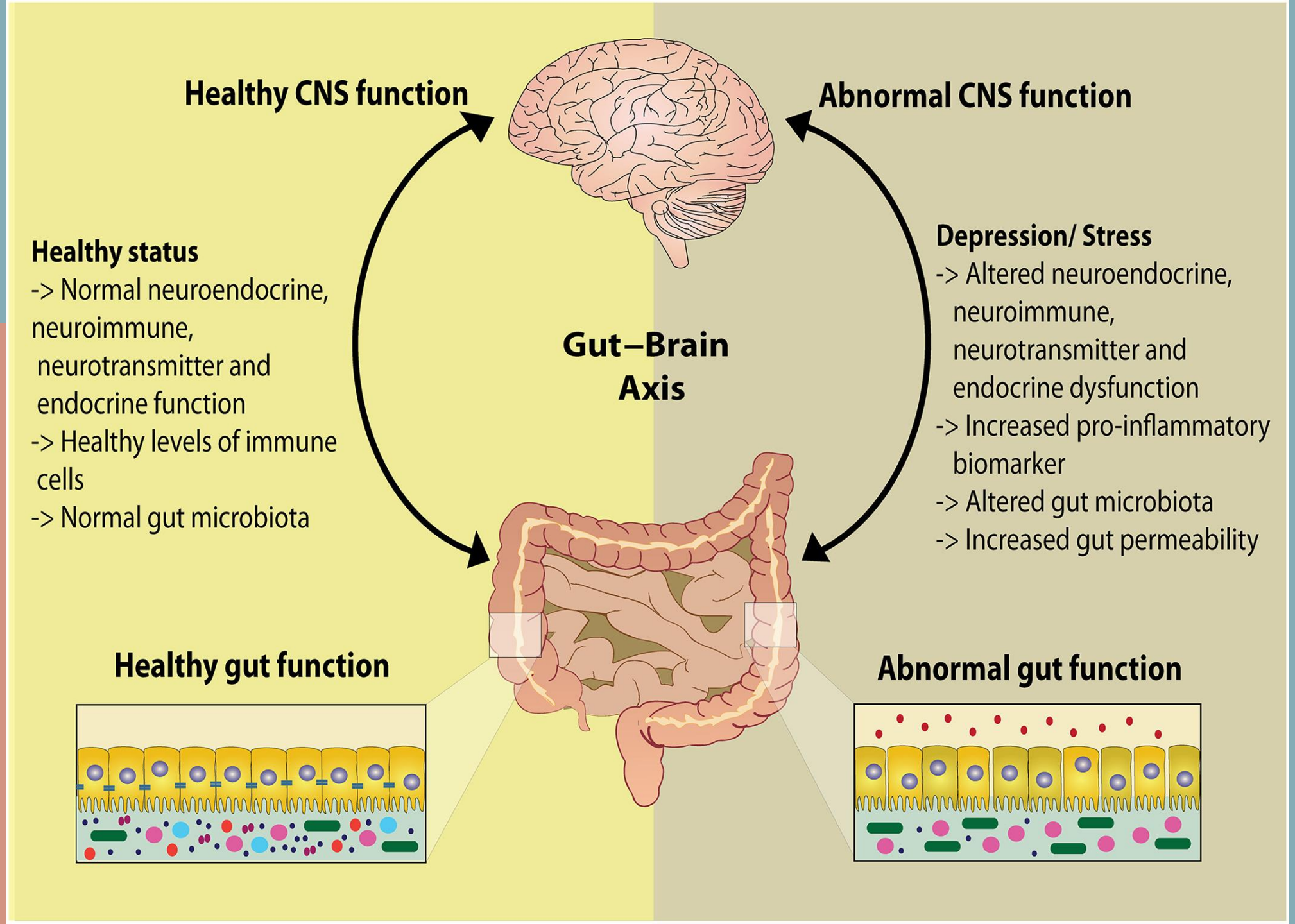
WHAT HAPPENS IN DYSBIOSIS?




Healthy CNS function
Abnormal CNS function
Healthy status
-> Normal neuroendocrine, neuroimmune, neurotransmitter and endocrine function
-> Healthy levels of immune cells
-> Normal gut microbiota
Gut–Brain Axis
Depression/ Stress
-> Altered neuroendocrine, neuroimmune, neurotransmitter and endocrine dysfunction
-> Increased pro-inflammatory biomarker
-> Altered gut microbiota
-> Increased gut permeability
Healthy gut function
Abnormal gut function

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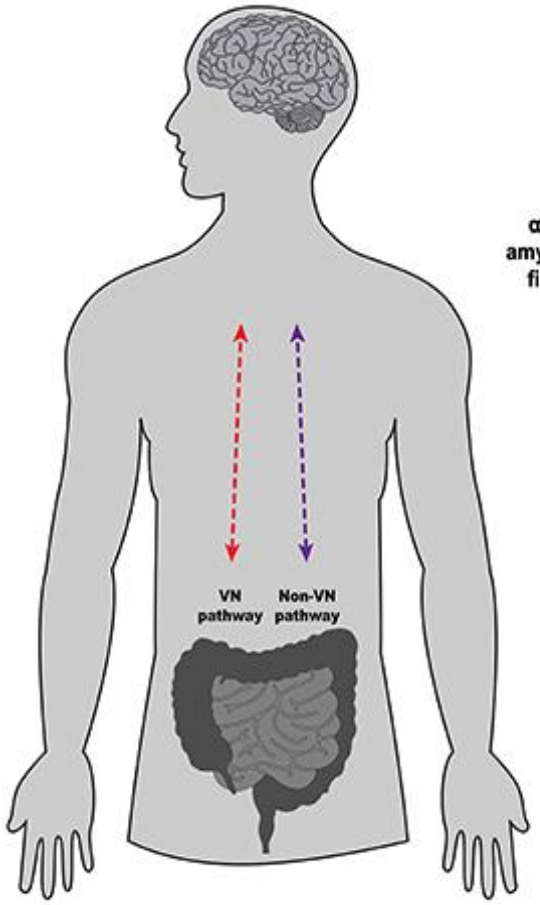
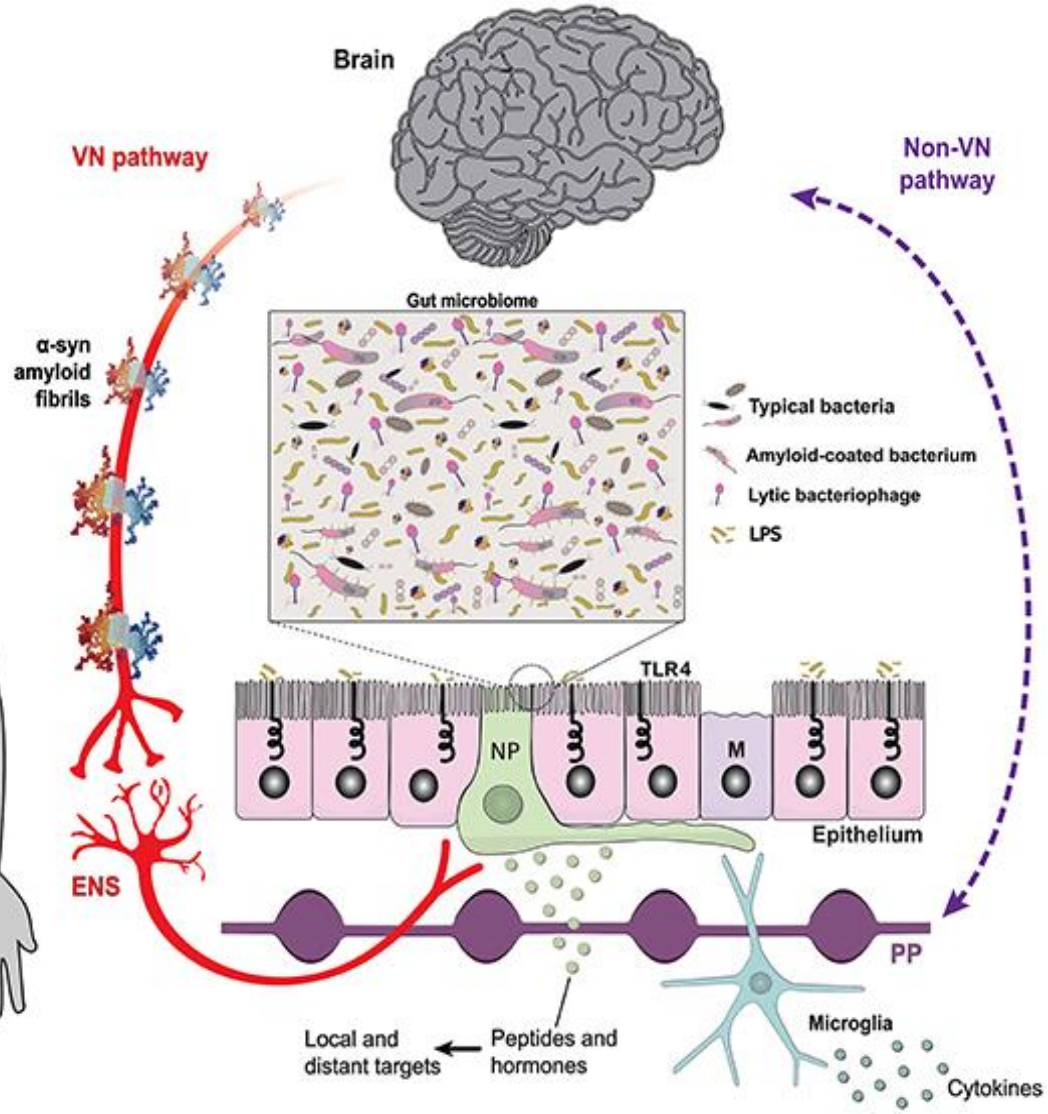
Gut and Parkinson's disease





More than 4 million papers on PD and gut dysfunction

Constipation may precede symptoms by at least a decade

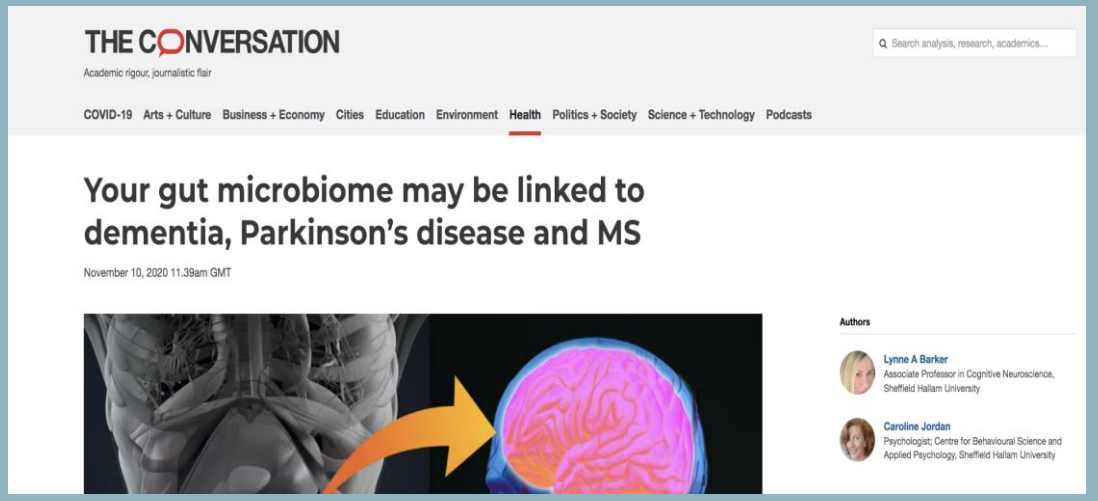
James Parkinson recognized gut problems as core symptom of shaking palsy

Symptoms may vary across people and across lifespan

Santos, S, F., de Oliveira, H. L., Yamada, E. S., Neves, B. C. & Pereira. (2019). A. The Gut and Parkinson's Disease—A Bidirectional Pathway. Frontiers in Neurology, Vol 10. DOI=10.3389/fneur.2019.00574

Our study: RCT feasibility study with probiotic and placebo groups

- 15 patients with PD assigned to probiotic or placebo group
- Fecal sample at baseline and 12 weeks
- Evidence of a PD *signature* approx. 100 species
- Dysbiotic microbiome but groups not different at baseline species prevalence
- Changes in prevalence and abundance of beneficial microbes between the two groups at 12 weeks



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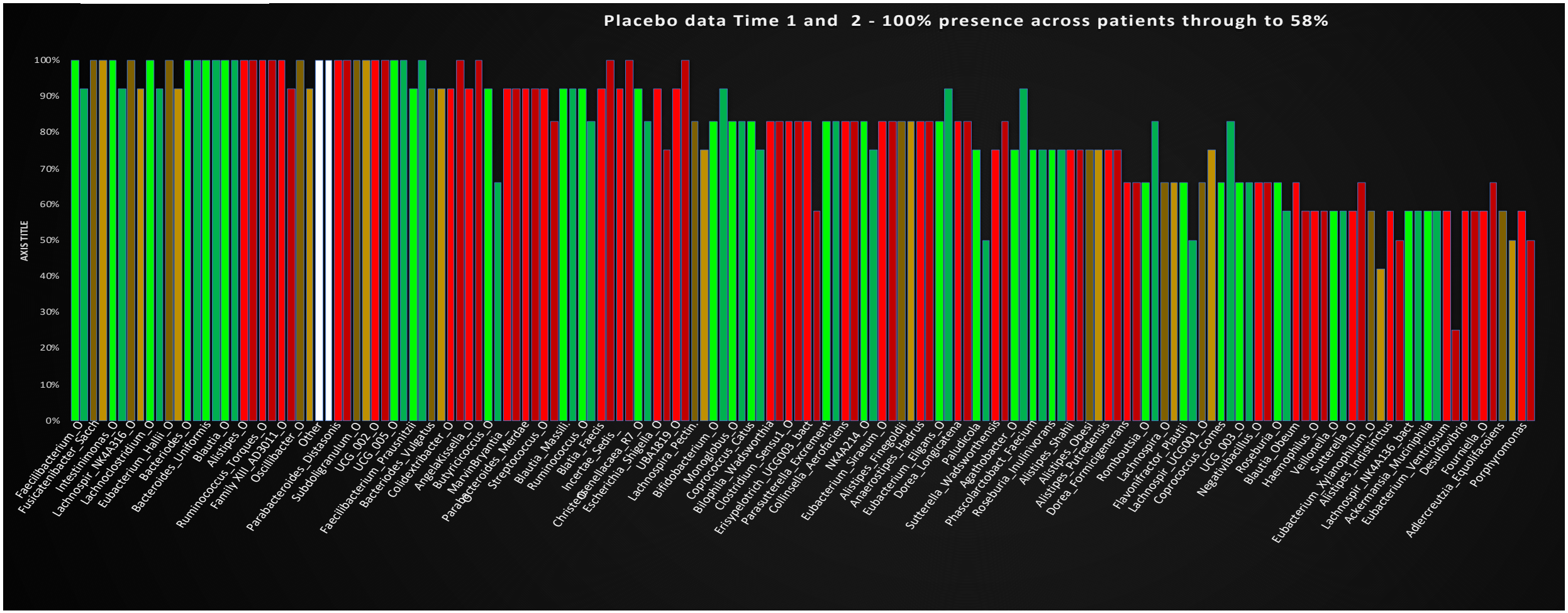
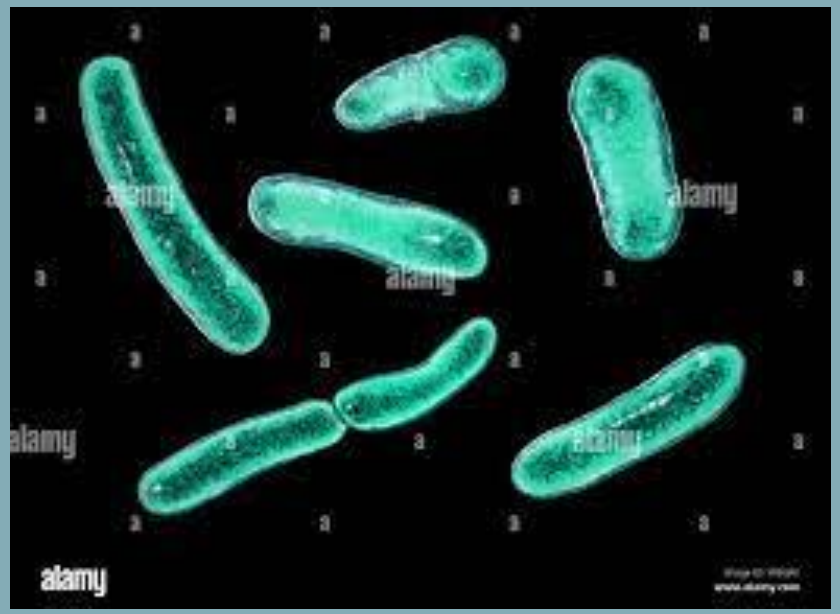

Placebo data Time 1 and 2 - 100% presence across patients through to 58%
AXIS TITLE
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Faecilibacterium_O
Fusicatenibacter_Sacch
Intestinimonas_O
Lachnospir_NK4A316_O
Lachnoclostridium_O
Eubacterium_Halli_O
Bacteriodes_O
Bacteroides_Uniformis
Blautia_O
Alistipes_O
Ruminococcus_Torques_O
Family XIII_AD3011_O
Oscillibacter_O
Other
Parabacteroides_Distasonis
Subdoligranulum_O
UCG_002_O
UCG_005_O
Faecilibacterium_Prausnitzii
Bacteriodes_Vulgatus
Colidextribacter_O
AngelaKissella_O
Butyricicoccus_O
MarvinBryantia_
Parabacteroides_Merdae
Streptococcus_O
Blautia_Massili.
Ruminococcus_O
Blatia_Faecis
Incertae_Sedis_
Christensenellaceae_R7_O
Escherichia_Shigella_O
UBA1819_O
Lachnospira_Pectin.
Bifidobacterium_O
Monoglobus_O
Coprococcus_Catus
Bilophila_Wadsworthia
Clostridium_Sensu1_O
Erisypelotrich_UCG003_bact
Parasutterella_Excrement
Collinsella_Aerofaciens
NK4A214_O
Eubacterium_Siraeum_O
Alistipes_Finegoldii
Anaerostipes_Hadrus
Eubacterium_Eligans_O
Dorea_Longicatena
Paludicola
Sutterella_Wadsworthensis
Agathobacter_O
Phascolarctobact_Faecium
Roseburia_Inulinivorans
Alistipes_Shahii
Alistipes_Obesi
Alistipes_Putredensis
Dorea_Formicigenerans
Romboutsia_O
Lachnospira_O
Flavonifractor_Plautii
Lachnospir_UCG001_O
Coprococcus_Comes
UCG_003_O
Negativibacillus_O
Roseburia_O
Blautia_Obeum
Haemophilus_O
Veillonella_O
Sutterella_O
Eubacterium_Xylanophilum_O
Alistipes_Indistinctus
Lachnospir_NK4A136_bact
Ackermansia_Muciniphila
Eubacterium_Ventriosum
Desulfovibrio
Fournierella_O
Adlercreutzia_Equolifacoiens
Porphyromonas

CONTROL GROUP DIMINISHED PREVALENCE OF GOOD BACTERIA AFTER 12 WEEKS



Species	Function	Probiotic Group
Faecalibacterium ↓	Most abundant and important commensal bacteria of the human gut microbiota	✓
Intestinimonas ↓	Oxalate & Butyrate	✓
Lachnoclostridium ↓	Reduced in bowel cancer	✓
Butyricicoccus ↓	Butyrate producer natural probiotic	✓
Christensenellaceae R-7 group ↓	Associated with low BMI	↓
Coprococcus_catus ↓	Hydrocarbon muncher	✓
NK4A214 group ↓	Prevent Type 2 diabetes	✓
Paludicola ↓	Hydrocarbon muncher	↓
Flavonifractor_plautii ↓	Anti-inflammatory properties	✓
Roseburia ↓	prevents intestinal inflammation	↓

Other Conditions

Condition	Presenting gut symptoms	Authors
Multiple Sclerosis	Altered Microbiome compared to controls	Levi et al., 2021
Dementia	Gut barrier dysfunction	Stadlbauer et al., 2020
Chronic Kidney Disease	Altered Microbiome compared to controls	Li et al., 2019
Obesity	Altered Microbiome compared to controls	Companys et al., 2021
Schizophrenia	Altered Microbiome compared to controls	Zhu et al., 2021
Neurodevelopment disorders	Altered Microbiome compared to controls	Bojovic´ et al., 2020
Colorectal Cancer	Altered Microbiome	Coker et al., 2020
Gestational Diabetes	Altered Microbiome	Hassain et al, 2020

DIET AND THE MICROBIOME

- Know far less than we ought to about diet and MB
- Temporary change seems to have only temporary effects[1]
- Still do not know what constitutes gastrointestinal gravity and holds the MB in stasis – eubiotic or dysbiotic

[1]*Leeming et al., 2019, Nutrients 10.3390/nu11122862*

WHAT DO WE KNOW ABOUT DIETARY INTERVENTIONS?

- Permanent rather than transient changes to the core gut microbiota required for long-term impact on health outcomes
- Diet–microbe interventions must consider the capabilities of an individual to make sustainable dietary changes because change occurs 24-48 hours after dietary intervention but then MB reverts [1]
- Many factors affect efficacy of dietary interventions including diurnal fluctuations and individual variability

[1]*Sonnenburg J.L., Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature. 2016;535:56–64. doi: 10.1038/nature18846.*

OTHER FACTORS

[1]Kaczmarek and colleagues notes several species related to eating time.

[2]Collado et al., found that timing of meal affects salivary microbial profile in pro-inflammatory way, affecting body weight, cortisol rhythm, basal metabolic rate, glucose tolerance and body temperature

Effect of fasting or time-restricted feeding on the gut microbiota are still unknown

[1]Kaczmarek J.L., Musaad S.M., Holscher H.D. Time of day and eating behaviors are associated with the composition and function of the human gastrointestinal microbiota. Am. J. Clin. Nutr. 2017;106:1220–1231. doi: 10.3945/ajcn.117.156380.

[2]Collado M.C., Engen P.A., Bandín C., Cabrera-Rubio R., Voigt R.M., Green S.J., Naqib A., Keshavarzian A., Scheer F.A.J.L., Garaulet M. Timing of food intake impacts daily rhythms of human salivary microbiota: A randomized, crossover study. FASEB J. 2018;32:2060–2072. doi: 10.1096/fj.201700697RR.

HEALTHY FOOD: FIBRE

One study found fibre intake positively correlated with a change in abundance of 15% of the microbial community the following day [1]

A 2018 systematic review and meta-analysis observed the effect of fibre on the gut microbiota from 64 studies. Dietary fibre interventions, particularly fructans and galactooligosaccharides (GOS), were found to increase faecal abundance of Bifidobacterium and Lactobacillus species but did not affect alpha-diversity [2]

Johnson et al found that microbial composition related to food choices rather than the conventional nutrient profile typically used in nutrition research,

[1]David L.A., Materna A.C., Friedman J., Campos-Baptista M.I., Blackburn M.C., Perrotta A., Erdman S.E., Alm E.J. Host lifestyle affects human microbiota on daily timescales. Genome Biol. 2014;15:R89. doi: 10.1186/gb-2014-15-7-r89.

[2]So D., Whelan K., Rossi M., Morrison M., Holtmann G., Kelly J.T., Shanahan E.R., Staudacher H.M., Campbell K.L. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. Am. J. Clin. Nutr. 2018;107:965–983. doi: 10.1093/ajcn/nqy041

[3]Johnson A.J., Vangay P., Al-Ghalith G.A., Hillmann B.M., Ward T.L., Shields-Cutler R.R., Kim A.D., Shmagel A.K., Syed A.N., Walter J., et al. Daily Sampling Reveals Personalized Diet-Microbiome Associations in Humans. Cell Host Microbe. 2019;25:789–802. doi: 10.1016/j.chom.2019.05.005

PREBIOTICS AND PROBIOTIC

Only short-term effects documented as with diet: because a healthy gut may have no biological niche for species engraftment

Not known whether there can be LT effects in dysbiotic gut

While probiotics may be transient, they have the capacity to alter the composition of the gut microbiota, in turn influencing the production of beneficial fermentation-derived metabolites

In addition, clinical effects have been shown without evidence of colonisation in probiotic studies [1]

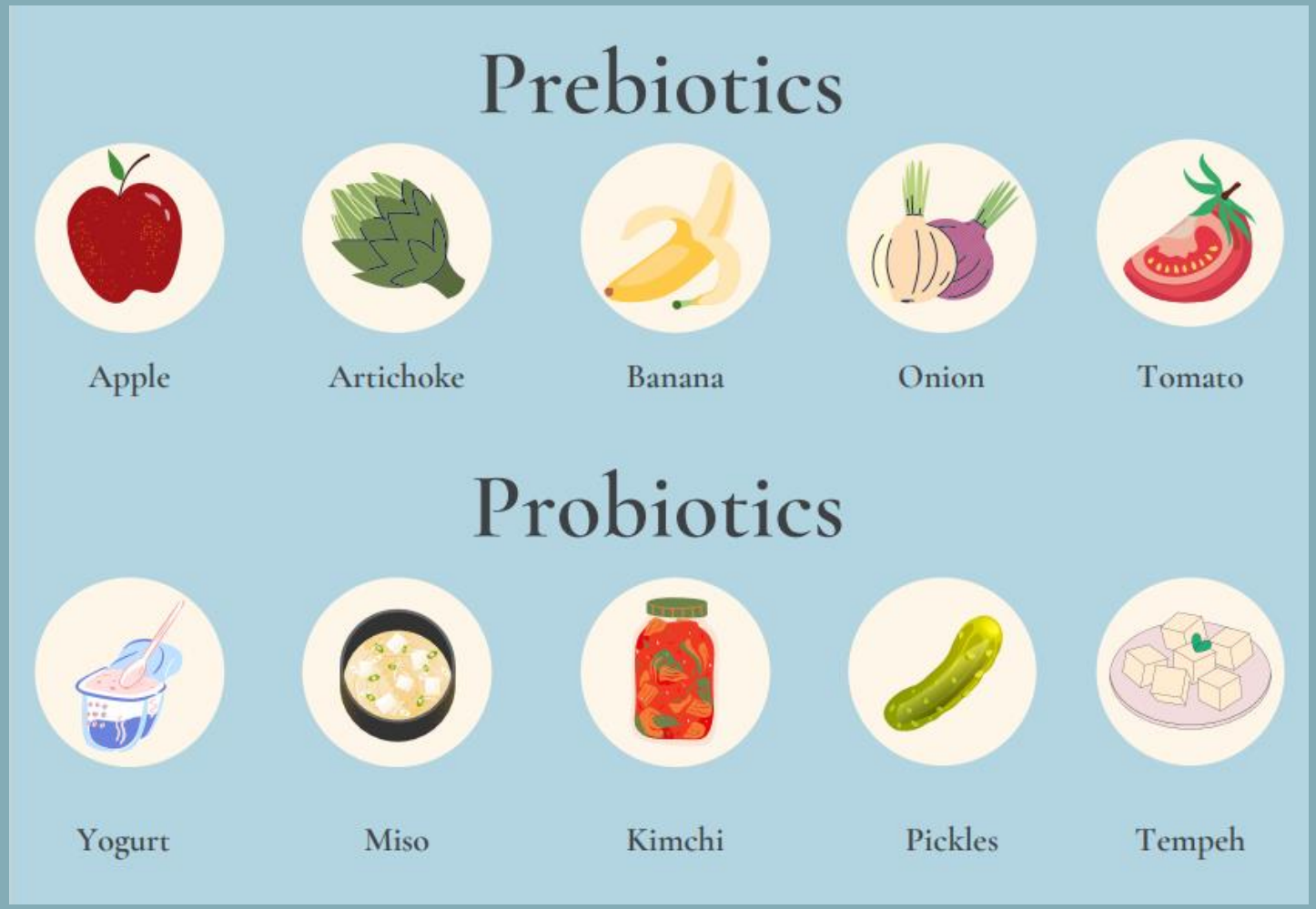
[1]*Sanders M.E., Merenstein D., Merrifield C.A., Hutkins R. Probiotics for human use. Nutr. Bull. 2018;43:212–225. doi: 10.1111/nbu.12334.*

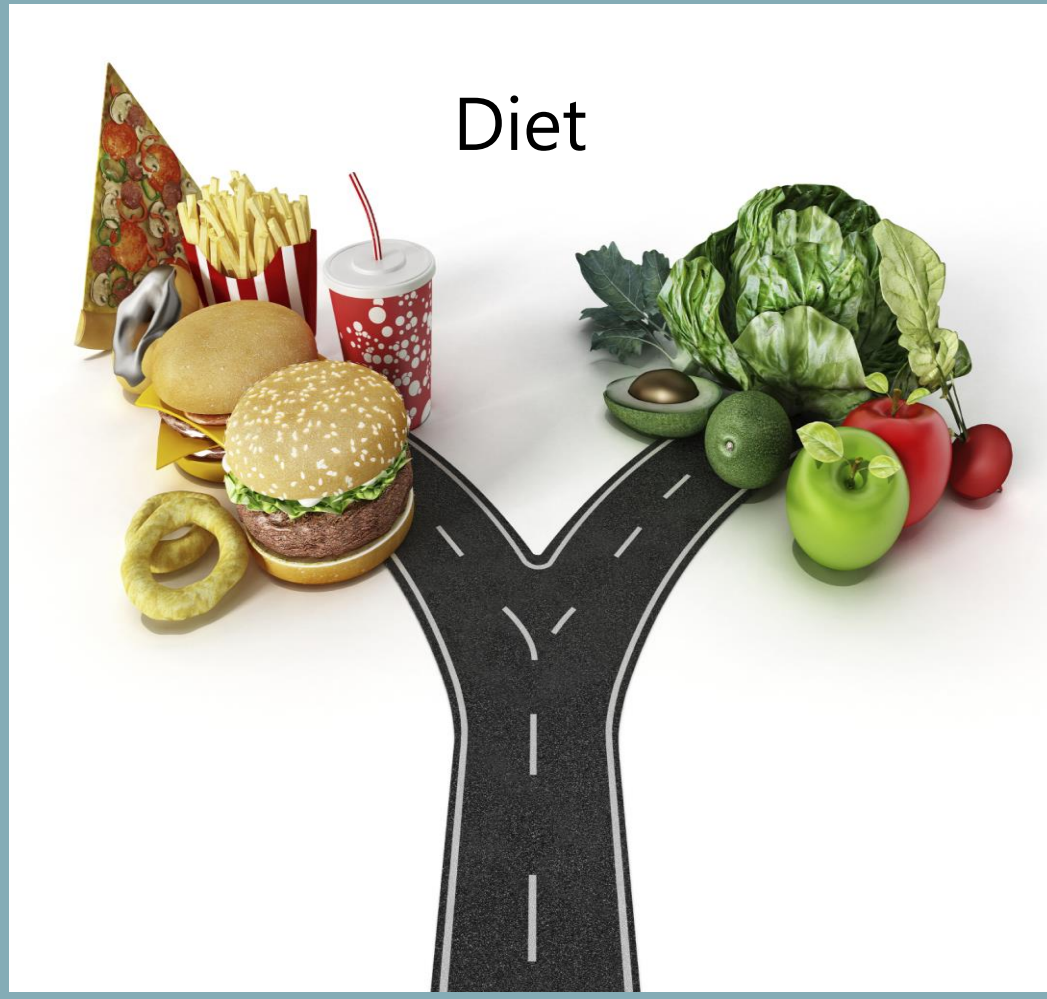
DYSBIOTIC GUT

Presents special case

Must be improved to create a biological niche and encourage engraftment of new species (beneficial)

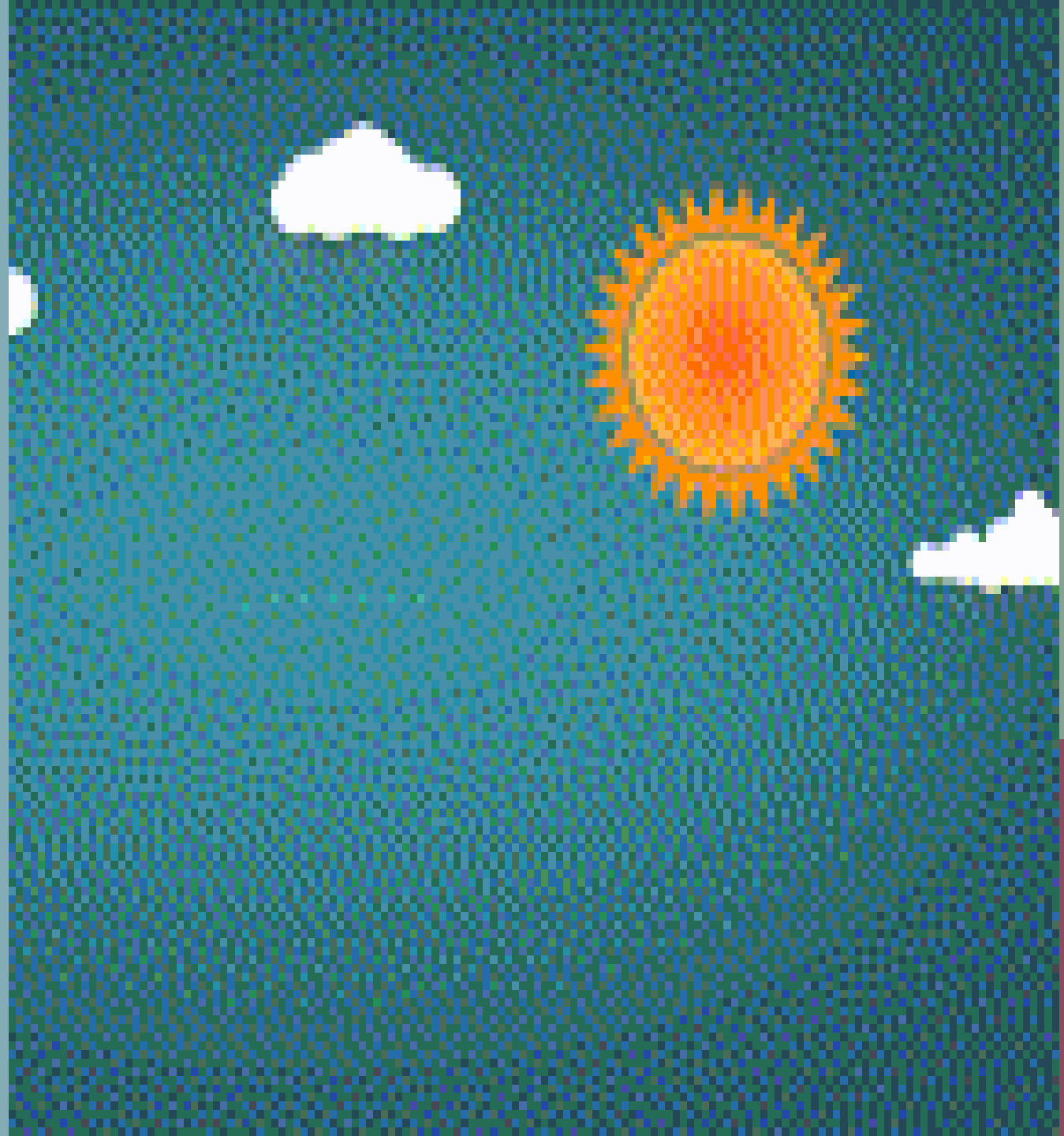
THREE-PRONGED APPROACH





OTHER FACTORS

Sunshine
Fresh air
Diurnal fluctuations
Sleep
Eating times and patterns
Exercise
Long term sustainable change



SUMMARY

1. Gut brain axis potential role in many conditions

2. Eubiosis and dysbiosis important clinical markers

3. Evidence based treatment includes prebiotic, probiotics, high fibre diet, exercise, limiting toxins and antibiotics

LEARNING OUTCOMES

Consider gut symptoms and dysbiosis in the context of current research

Consider gut dysbiosis alongside non-gut based symptoms in presenting patients

Consider recommending dietary change and supplementation for gut dysbiosis

Supported by Symprove

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