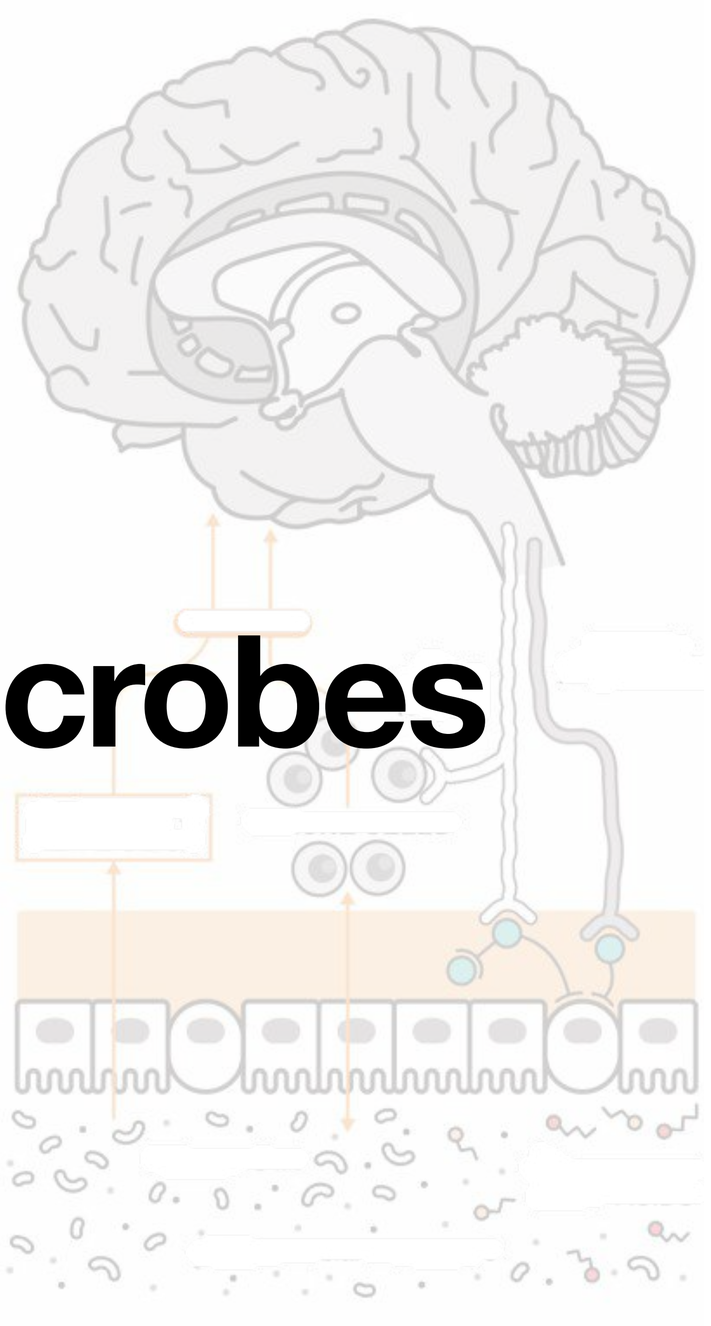
BANT AGM & Conference

MENTAL HEALTH,
PRECISION NUTRITION,
& LIFESTYLE MEDICINE:
Translating Evidence to
Clinical Practice



Mind, Brain, and Microbes

The Impact of the Gut Microbiota on Human Health and Behaviour

Dr Miguel Toribio-Mateas, May 2022

Dr Miguel Toribio-Mateas

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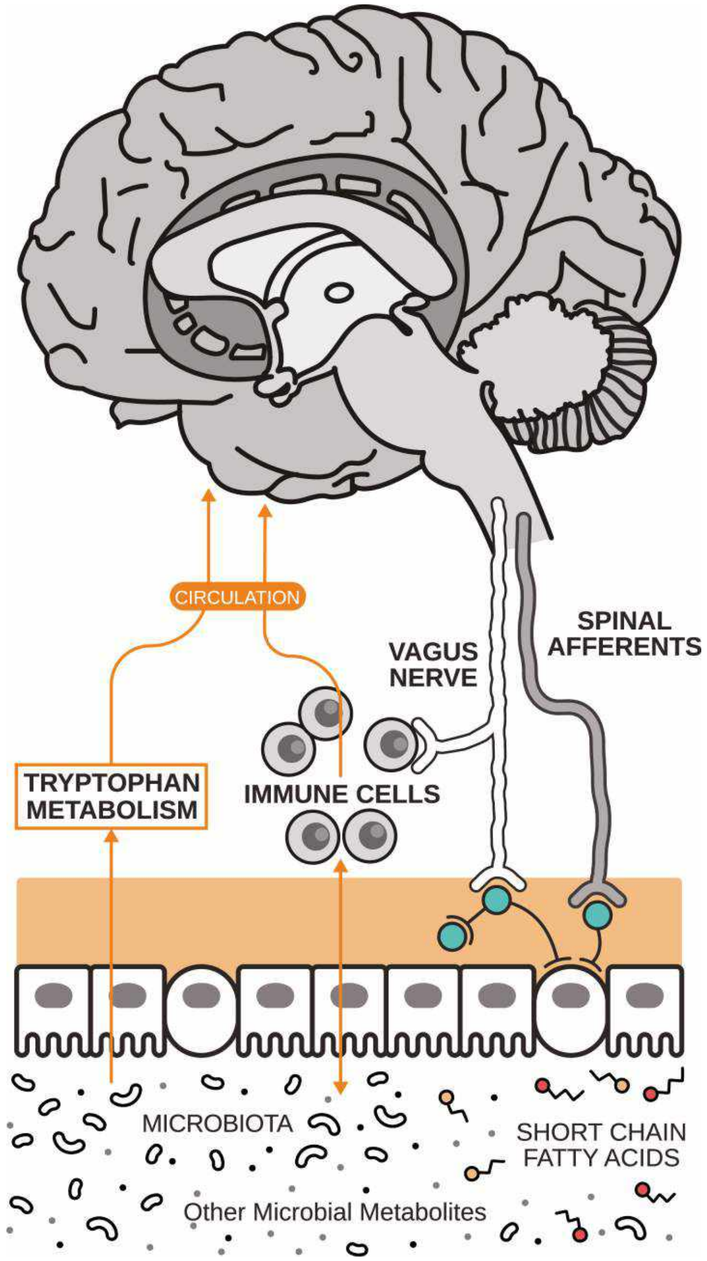


Key question 1

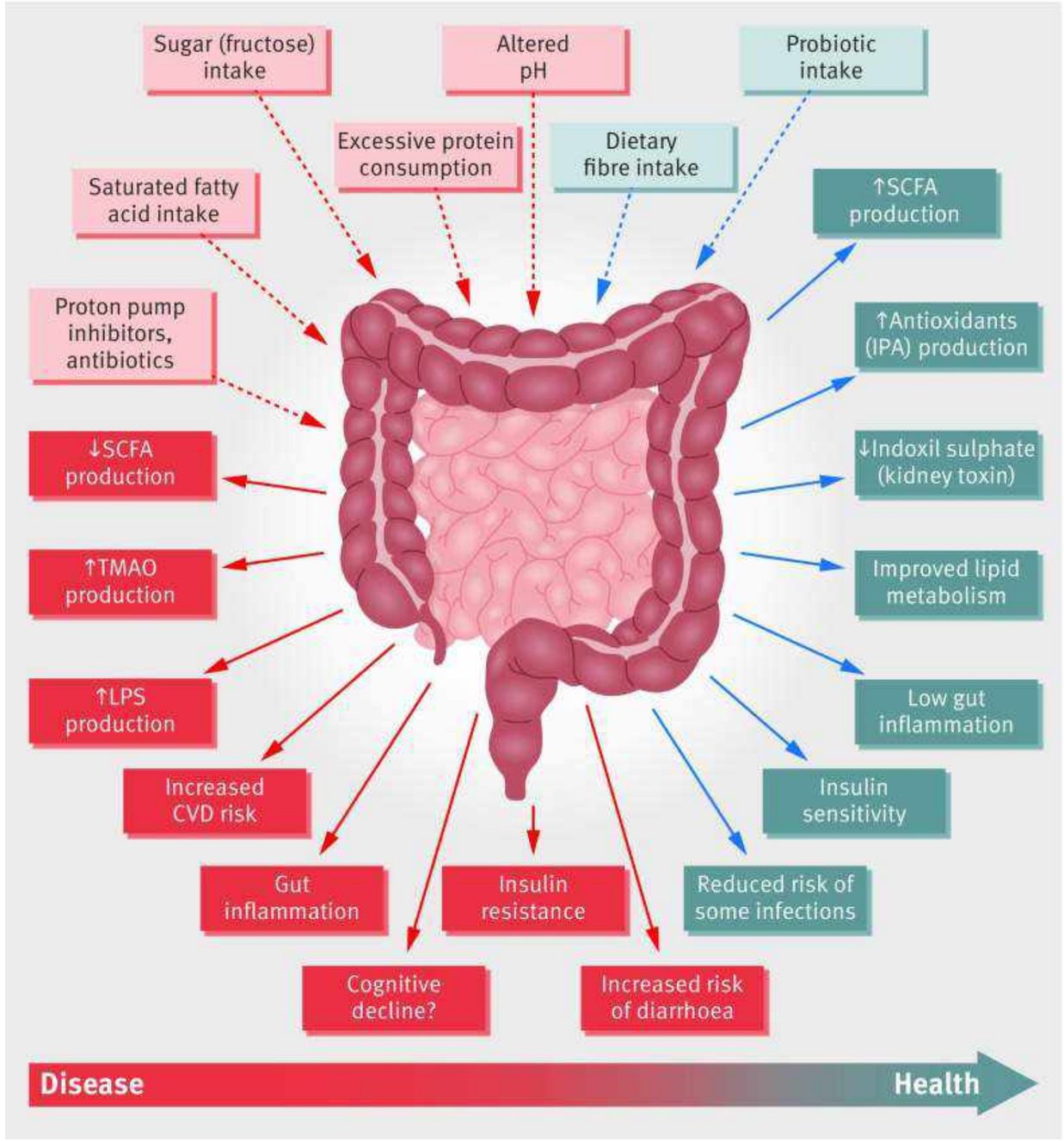
How is the gut microbiota to relevant to brain / mental health?

3 Bioessays. 2018 Jan;40(1). doi: 10.1002/bies.201700172.

What is the gut microbiome?

The microbiome refers to all microorganisms in or on their host as well as their genetic material. The microbiota, on the other hand, defines the microbe population in a specific ecosystem, such as those populations found in the gut microbiota or skin microbiota.

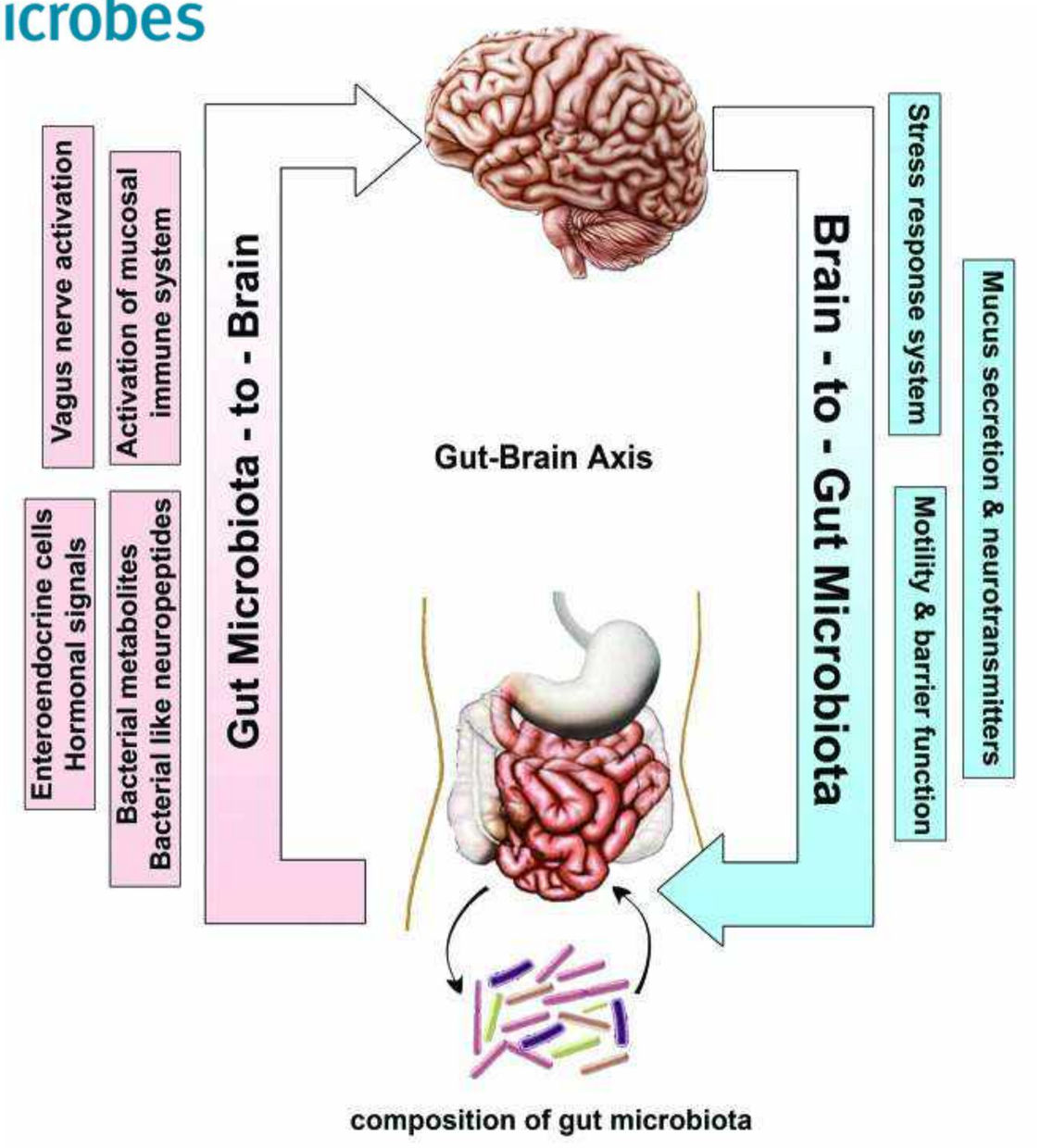
Within the gut, there are approximately 10^{14} (100 trillion) microorganisms, which is around 10 fold more cells than there are cells in the human body.



The gut microbiome plays a key role in the balance between health and disease throughout the whole of the body.

BMJ. 2018 Jun 13;361:k2179.

gut microbes

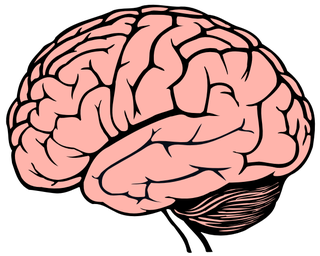


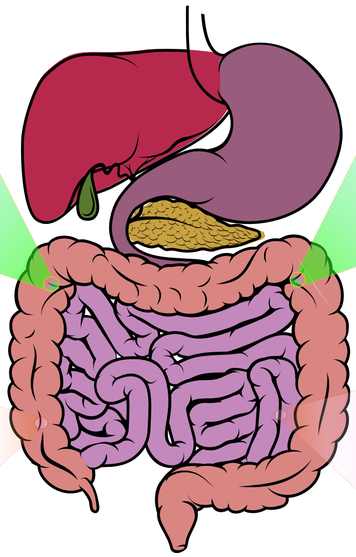
Principal mechanisms in microbiota-gut-brain axis communication

Gut Microbes. 2012 Jul-Aug;3(4):366-73. doi: 10.4161/gmic.21287

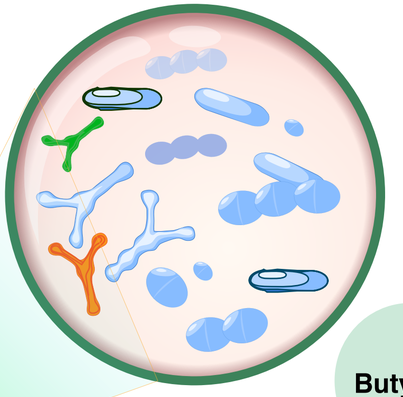
Mediterranean-style diet, rich in varied fresh produce

Diet rich in ultra-processed foods





Eubiosis



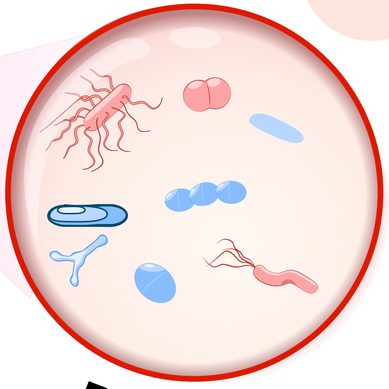
▲ Neuroplasticity
Short-chain fatty acids
▼ Microbial diversity, e.g.
Bifidobacteria, Bacteroides, Prevotella

▲ Firmicutes,
Beta-glucoronidase
▼ Zonulin, i.e. leaky gut
Glial activation

Butyrate

Acetate

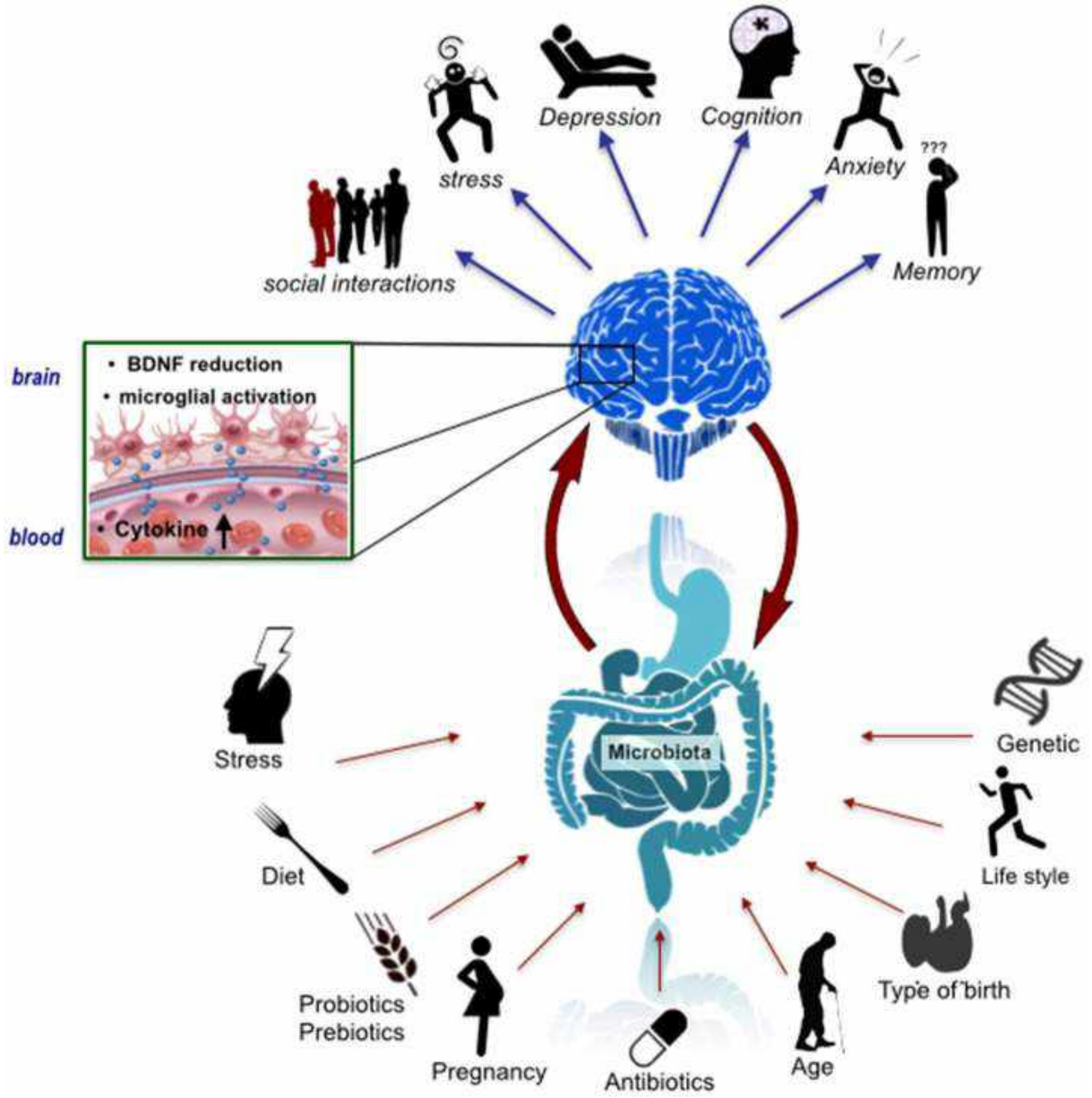
Propionate



Dysbiosis

▼ Neuroplasticity
Short-chain fatty acids
▼ Microbial diversity, e.g.
Bifidobacteria, Bacteroides, Prevotella

▲ Firmicutes,
Beta-glucoronidase,
▼ Zonulin, i.e. leaky gut
Glial activation



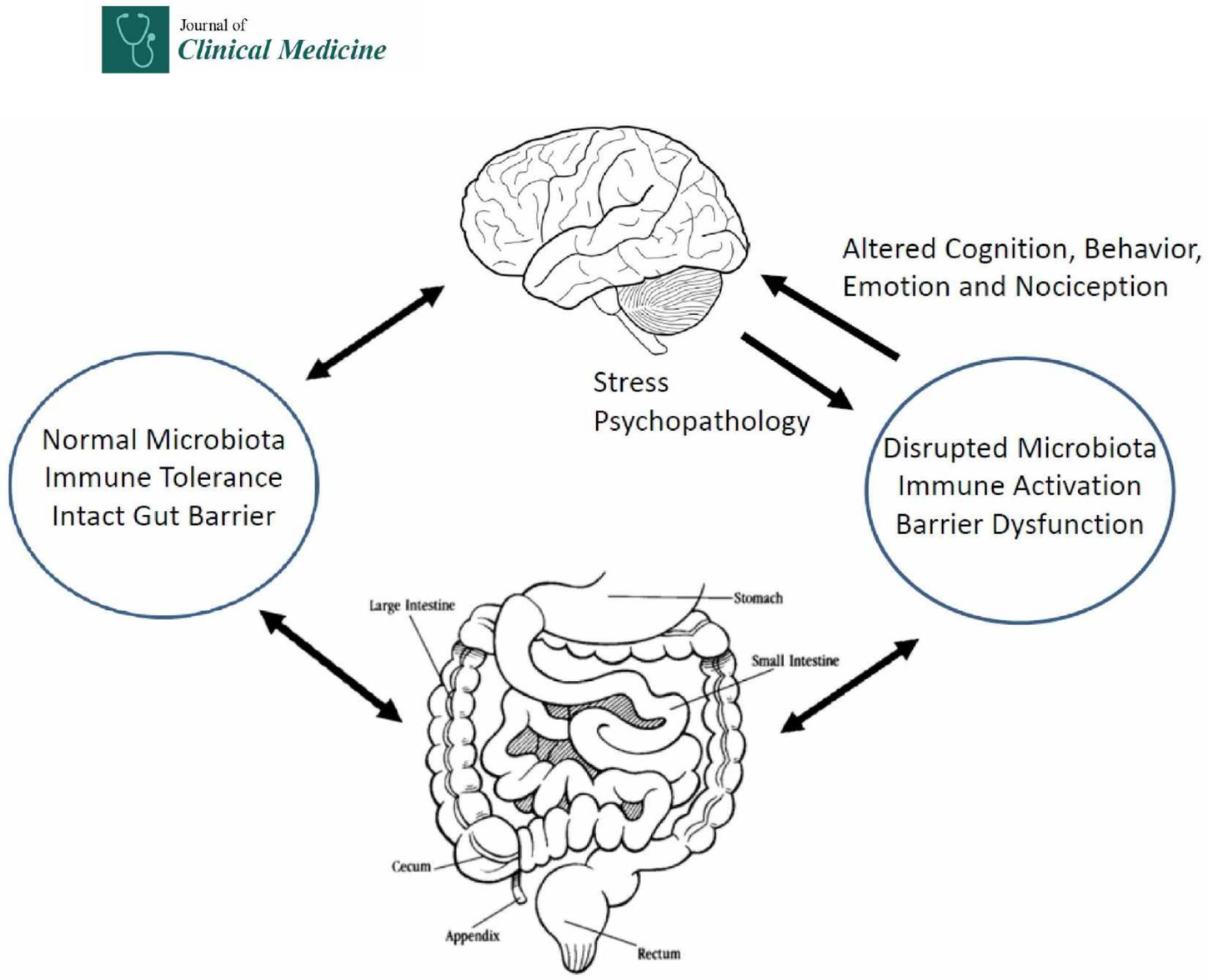
Key question 2

Are there specific microbial signatures for specific neuropsychiatric disorders?

Front Neurosci. 2017 Sep 15;11:490. doi: 10.3389/fnins.2017.00490

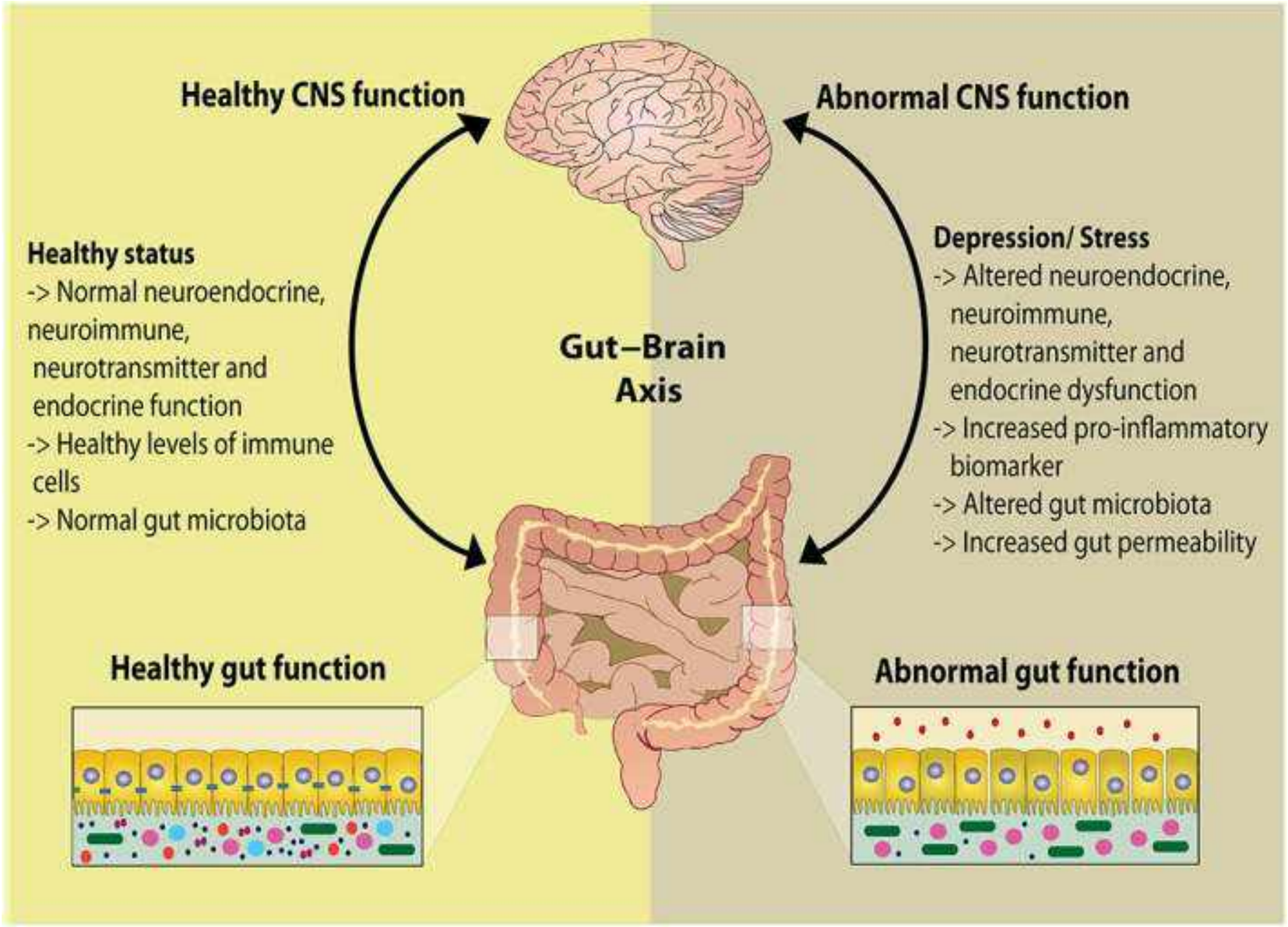
Normal vs abnormal microbiota

An abnormal microbiota is associated with a disrupted gut barrier and the activation of the mucosal immune system, leading to the release of inflammatory mediators and other neuroactive molecules into the systemic circulation from where they reach the brain, resulting in changes in cognition and behaviour.



J Clin Med. 2018 Jan 3;7(1):6. doi: 10.3390/jcm7010006

BJP British Journal of Pharmacology



Healthy vs abnormal gut–brain axis

In negative affective states such as stress, anxiety or depression, the expression of pro-inflammatory markers increases, gut microbiota and gut permeability are altered and the gut–brain axis is in a dysfunctional state.

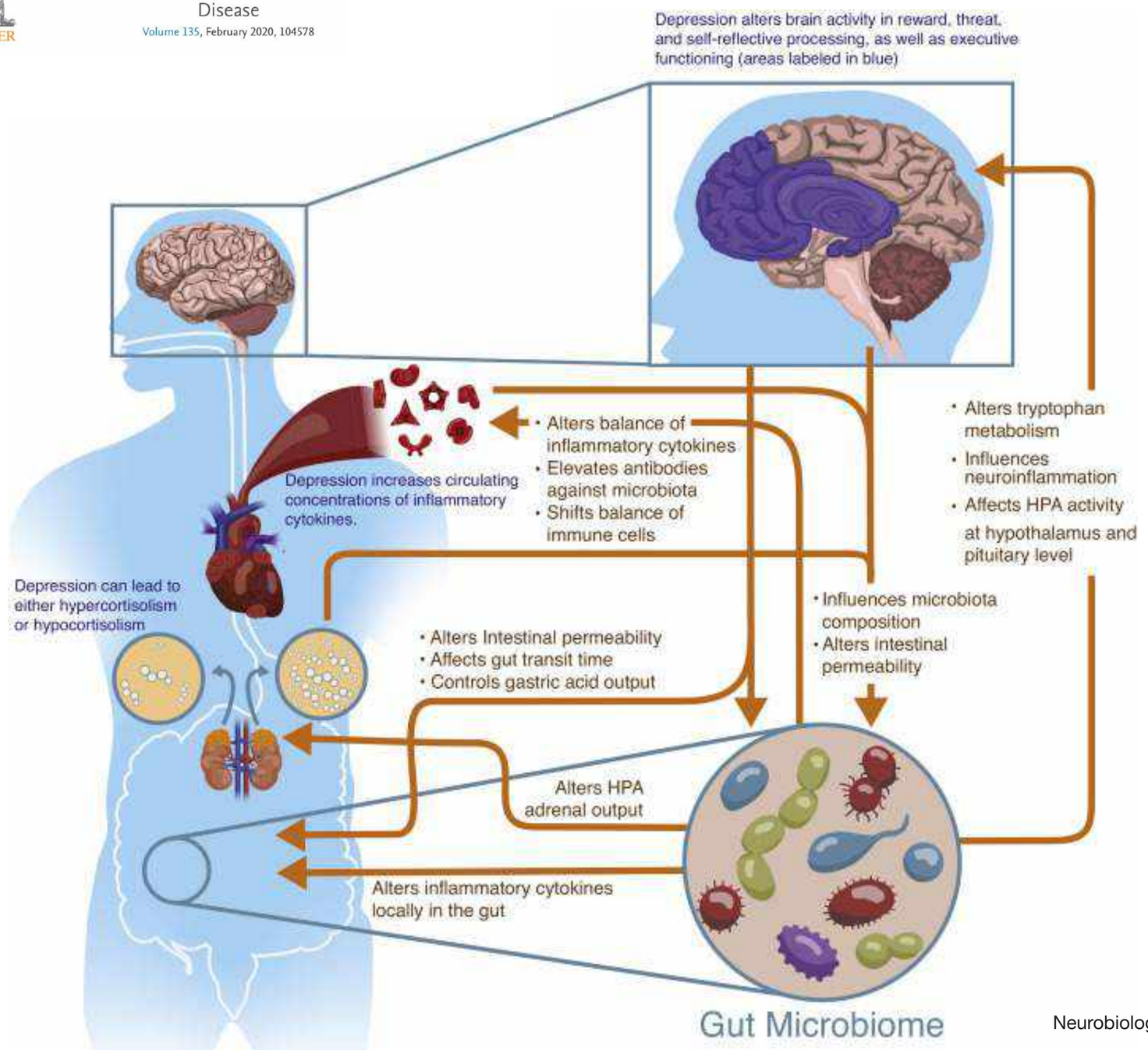
Br J Pharmacol. 2018 Dec;175(24):4430-4438. doi: 10.1111/bph.14127
10

Scope of the evidence reviewed

For the purpose of this presentation I have drawn on research examples on the relationship between the gut microbiome and the following research areas:

Depression, anxiety and mild cognitive impairment.

Neurobiology of Disease
Volume 135, February 2020, 104578



What is the role of the microbiome in the context of depression?

Exploratory human studies describing correlations/interactions between the gut microbiota and cognition, brain structure or function.

Author/Year	Participants/Sample (± SD)	Sex (M/F)	Study Design	Assessment	Main Findings Microbiome Link
Fernandez-Real et al. (2015) [29]	*n* = 19 obese; *n* = 20 non-obese patients; total age range 30–65 years (mean ± SD not specified)	Not known	Correlational (partial blind); microbiome markers of obese vs. non-obese patients	fMRI; Trail making test; 16S rRNA gene sequencing	Specific phyla linked to obesity, brain structures and trail map making
Anderson et al. (2017) [30]	*n* = 37 healthy (50–85 years; 64.6 ± 7.5 years)	10/27	Correlational; microbiome, sleep quality and cognition	Stroop Colour-Word (cog flexibility); PSQI (sleep)	Association with sleep quality and cognitive flexibility
Taylor et al. (2017) [31]—conf. abstract	*n* = 34 (25–45 years old); no average +SD given in conference abstract	0/34	Correlational: microbiota and cognition	Modified flanker test	Greater numbers of *Bacteriodetes* = cog. performance maintained with increasing task demand
Osadchiy et al. (2018) [12]	*n* = 63 healthy adults (29.4 ± 10.8 years)	29/34	Correlational; microbiome metabolites and links to brain networks, obesity and anxiety	HAD; YFAS; MRI (structural, functional, diffusion); faecal metabolomics	Faecal metabolites linked to brain connectivity, reward networks, and anxiety symptoms
Labus et al. (2017) [32]	*n* = 29 IBS patients (26.1 ± 5.7 years); *n* = 23 HC (26.0 ± 6.5 years)	17/35	Correlational: microbiome markers in IBS and correlates of brain structure	HADs + PHQ-15; ETI-SR; PSS; compact MRI 16S rRNA gene sequencing	Behavioural link to microbiome in IBS: sensory and salience network regions, early-life trauma

Nutrients. 2020 Sep 30;12(10):3009. doi: 10.3390/nu12103009

Journal of Affective Disorders
Volume 202, 15 September 2016, Pages 254-257

Possible association of *Bifidobacterium* and *Lactobacillus* in the gut microbiota of patients with major depressive disorder

Emiko Aizawa [a], Hirokazu Tsuji [c], Takashi Asahara [c], Takuya Takahashi [c], Toshiya Teraishi [a], Sumiko Yoshida [b], Miho Ota [a], Norie Koga [a], Kotaro Hattori [a], Hiroshi Kunugi [a]

- Depressive patients tend to have **significantly lower** Bifidobacterium counts and **lower** Lactobacillus counts than the controls.
- Decreased counts of these bacteria were associated with irritable bowel syndrome.

Interesting points:

- Study based on **43 patients** and **57 healthy** controls.
- Depressive symptoms assessed using the Hamilton depression rating scale 21-item version (HAM-D 21)

J Affect Disord. 2016 Sep 15;202:254-7. doi: 10.1016/j.jad.2016.05.038

Could probiotics help?

On the basis of this observation, would this be appropriate to intervene with a probiotic formula, with the aim to increase the abundance of Bifidobacterium and Lactobacillus?

Brain, Behavior, and Immunity
Volume 48, August 2015, Pages 186-194

Altered fecal microbiota composition in patients with major depressive disorder

Haiyin Jiang [a, 1], Zongxin Ling [a, 1], Yonghua Zhang [b, 1], Hongjin Mao [c], Zhanping Ma [d], Yan Yin [c], Weihong Wang [e], Wenxin Tang [c], Zhonglin Tan [c], Jianfei Shi [c], Lanjuan Li [a, 2] ✉, Bing Ruan [a] ✉

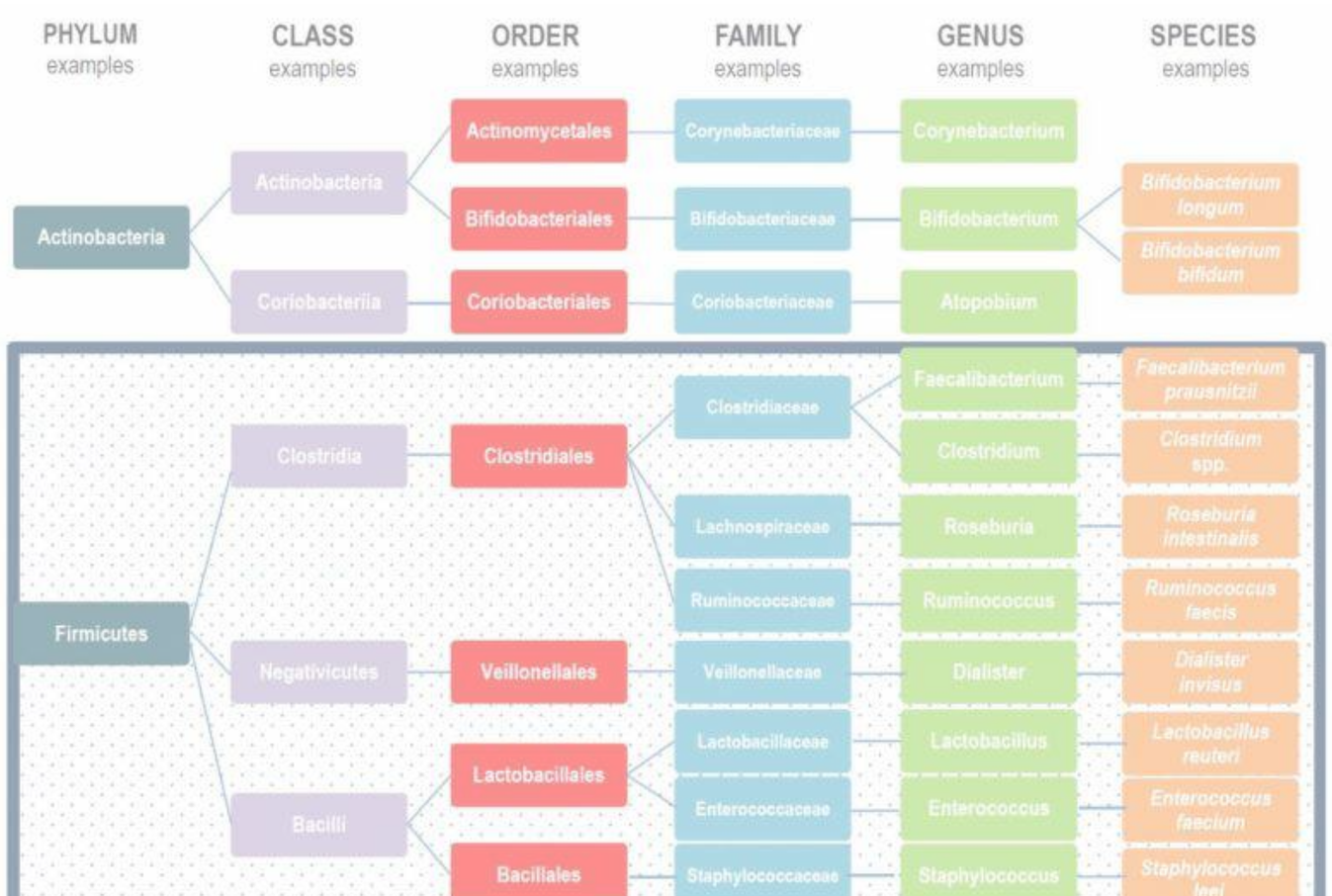
- Overrepresentation of Enterobacteriaceae and Alistipes but reduced levels of Lachnospiraceae.
- A negative correlation was observed between Faecalibacterium and the severity of depressive symptoms.

Interesting points:

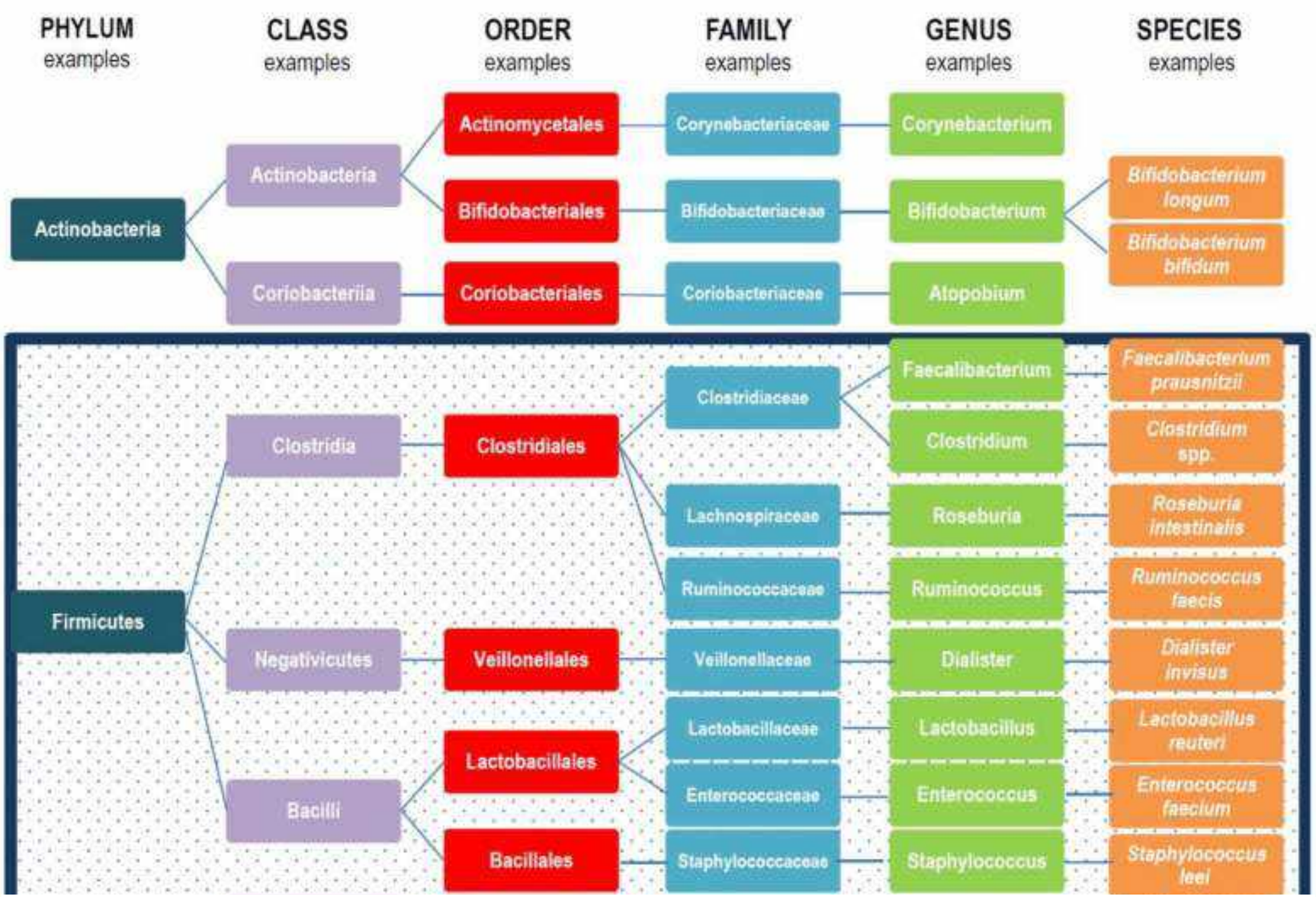
- Study based on **46 patients** and **30 healthy** controls.
- Depressive symptoms assessed using the Hamilton depression rating scale 24-item version (HAMDS) and the Montgomery–Asberg Depression Rating Scale (MADRS).

Brain Behav Immun. 2015 Aug;48:186-94. doi: 10.1016/j.bbi.2015.03.016

A little revision



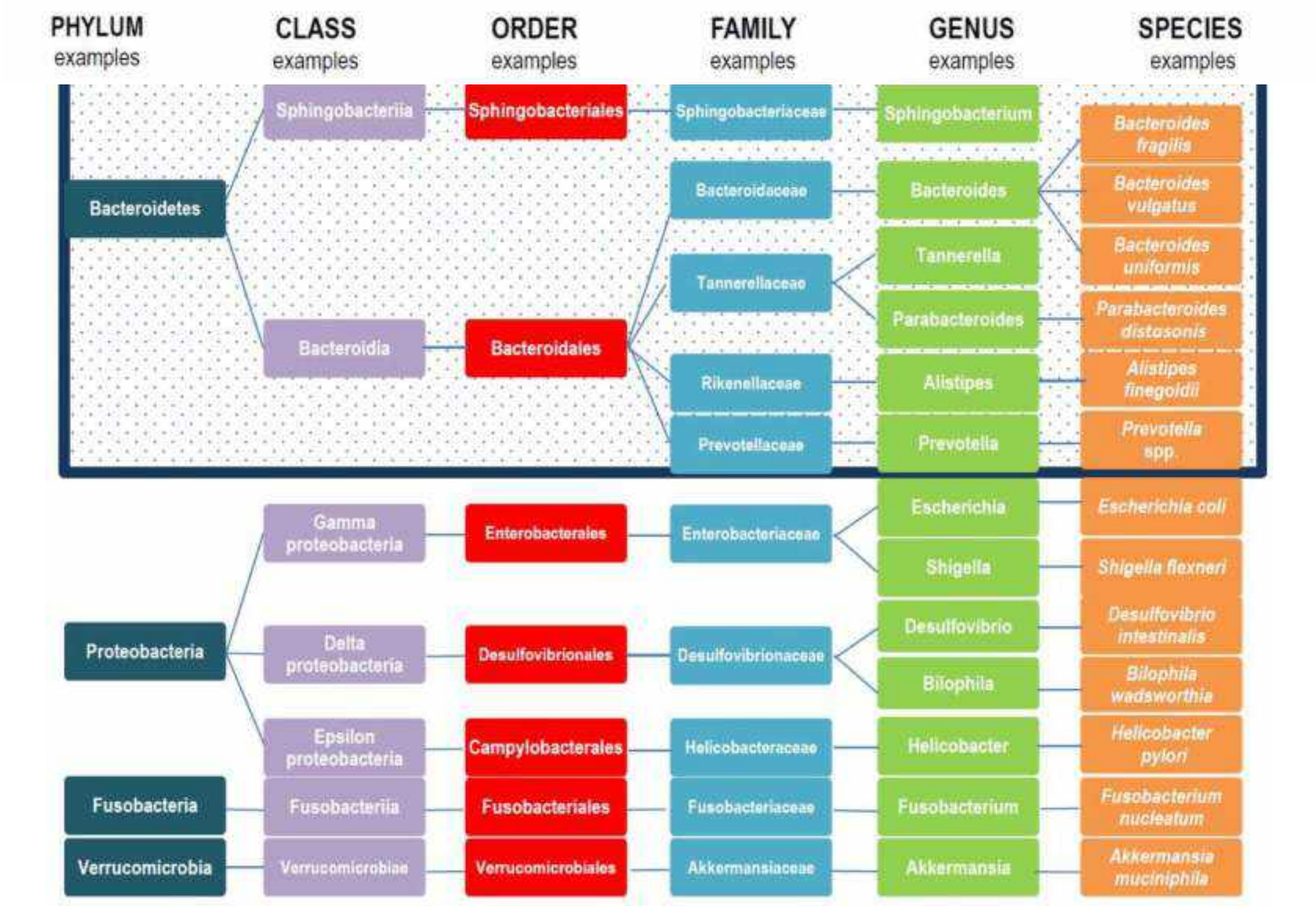
microorganisms



The core phyla are ***Firmicutes****,* ***Bacteroidetes****, and* ***Actinobacteria.*** *Between them, they represent ≈* ***90%*** *of the microbiota.*

Microorganisms. 2019 Jan 10;7(1):14. doi: 10.3390/microorganisms7010014

microorganisms



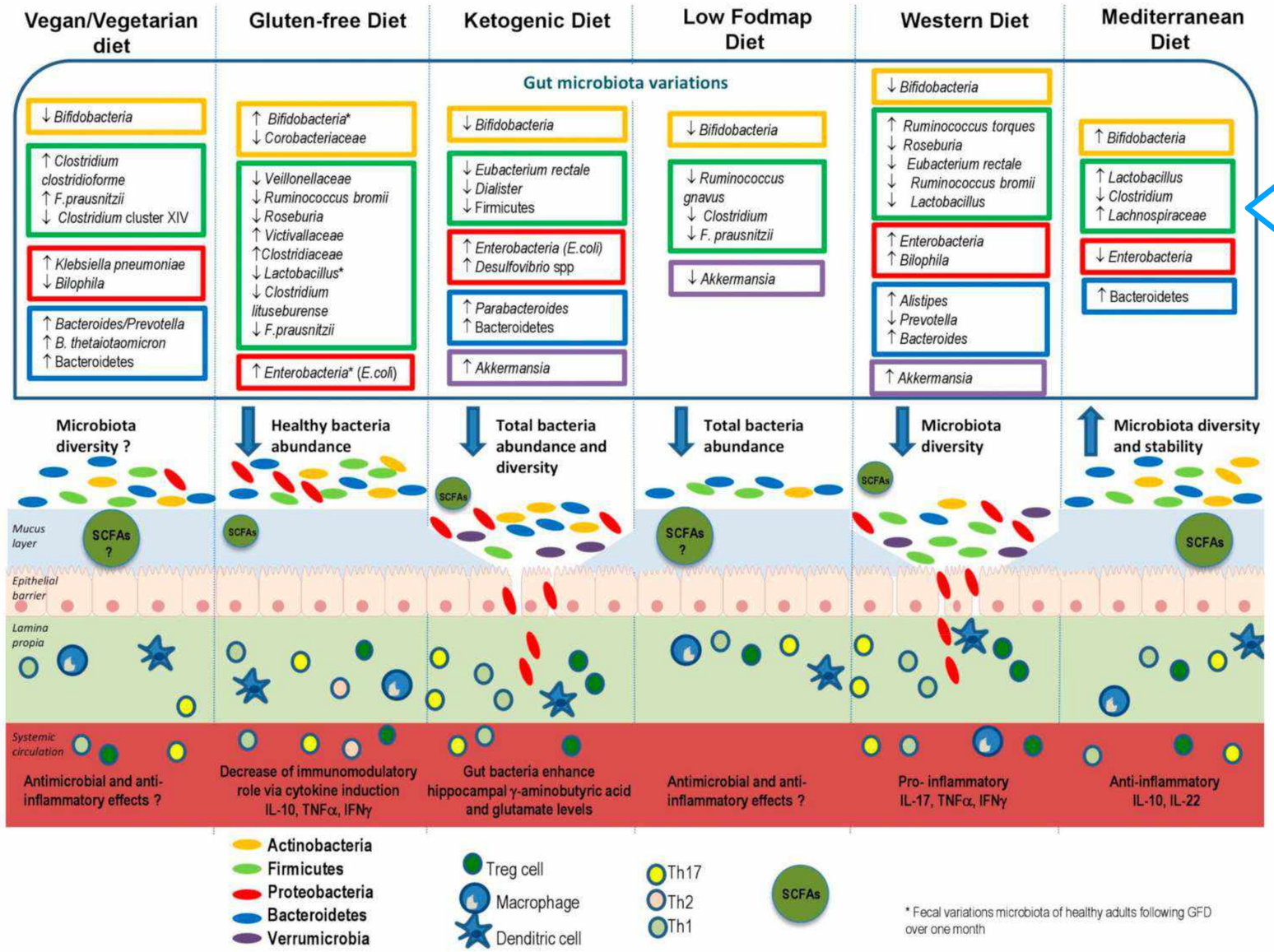
The remaining 10% belongs to the phyla ***Proteobacteria,*** ***Verrucomicrobia,*** *and* ***Fusobacteria.***

Microorganisms. 2019 Jan 10;7(1):14. doi: 10.3390/microorganisms7010014

Questions to ponder

- Lachnospiraceae is a family of microbes that includes the butyrate-producing *Faecalobacterium* and *Roseburia*, and the acetate-producing *Eubacterium hallii* group.
- All three genera are known to benefit from fibre and polyphenol-rich dietary interventions, e.g. using a Mediterranean-type diet, which has been seen to results in reduced Enterobacteriaceae, and in improved inflammatory and metabolic status.
- **There is no substantial evidence that Lachnospiraceae benefit from probiotic supplementation, but they do respond to dietary interventions.**

nutrients



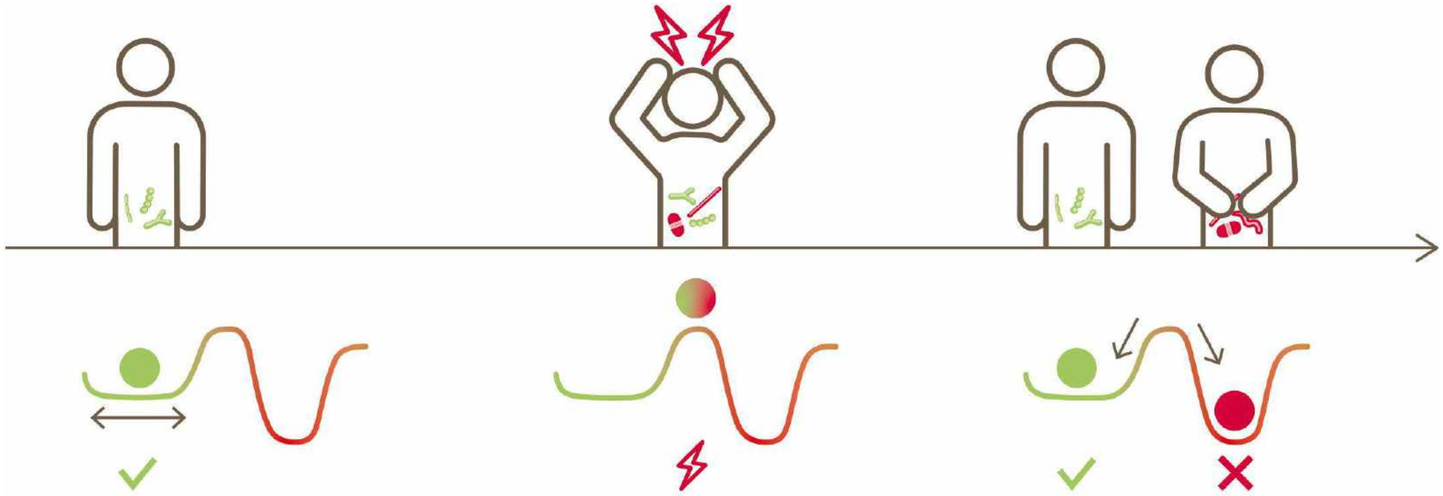
In fact, the evidence to support how different types of dietary interventions may be used to manipulate the microbiota gut-brain axis is abundant.

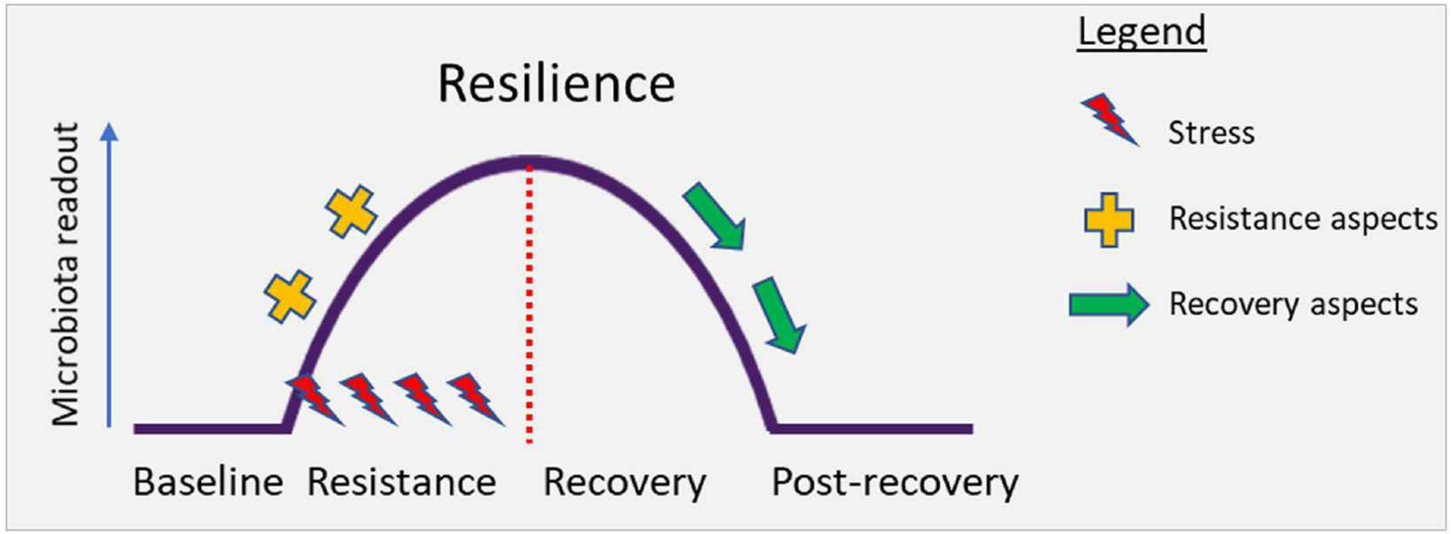
Of special interest is the value of a Mediterranean-type diet on the bacterial markers discussed on this slide.

frontiers in Microbiology | Microbial Symbioses

Gut Microbiota Resilience: Definition, Link to Health and Strategies for Intervention

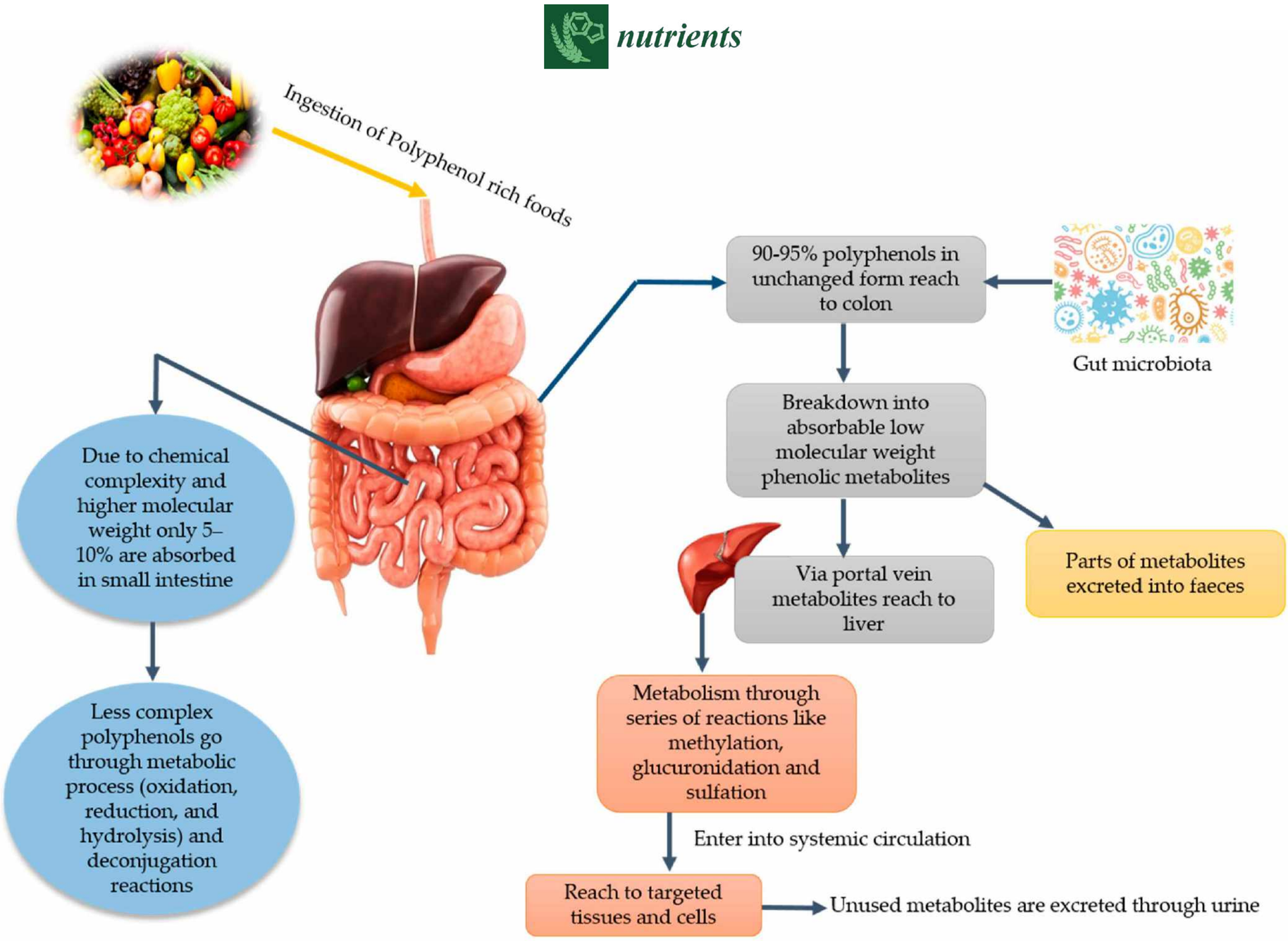
Shaillay Kumar Dogra[1], Joel Doré[2] and Sami Damak[1*]

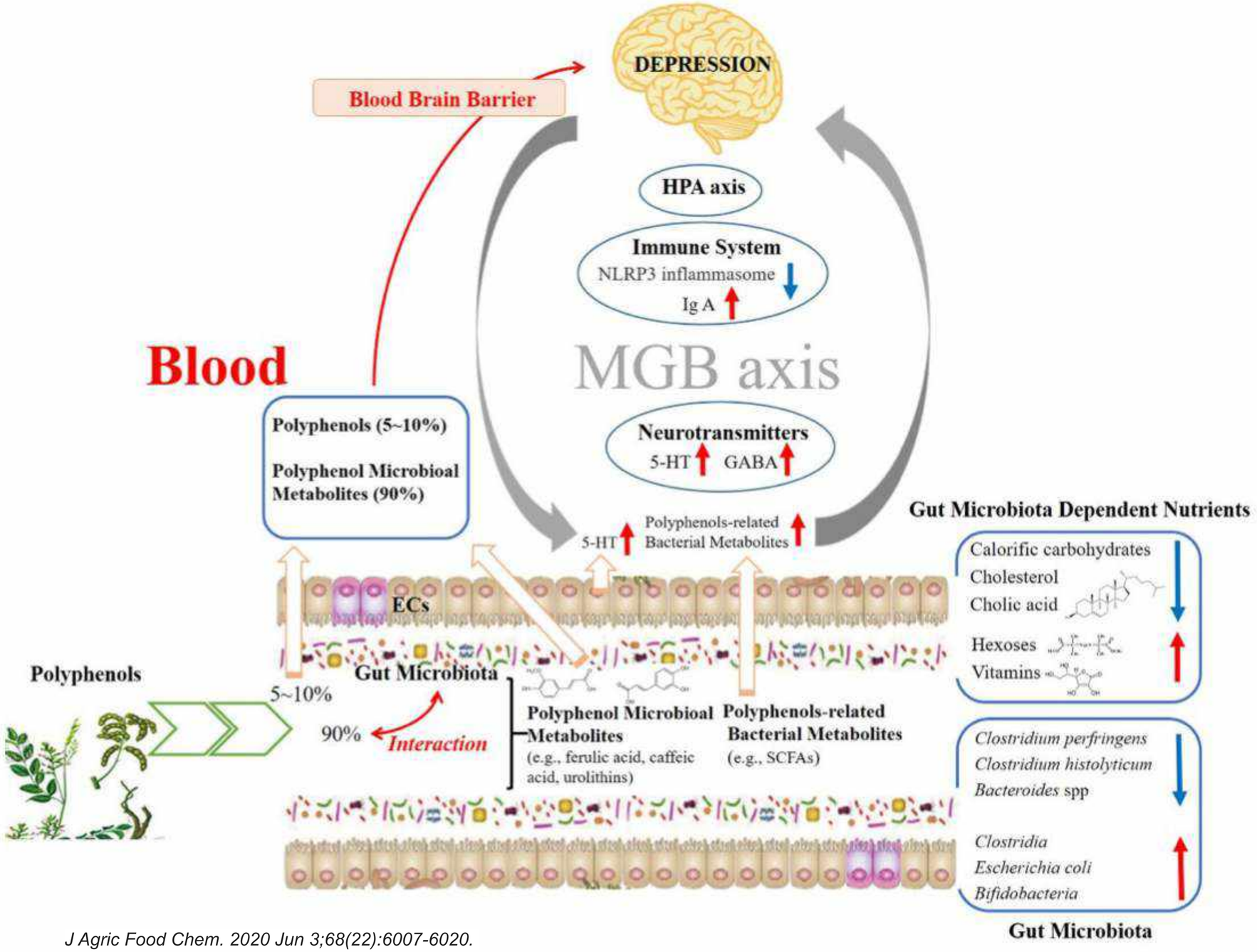




Front Microbiol. 2020;11:572921

Especially rich in the Mediterranean diet are dietary polyphenols, classed as *prebiotics*, and known to elicit significant changes in gut microbiota composition.





J Agric Food Chem. 2020 Jun 3;68(22):6007-6020.

The role of these plant-based nutrients in modulating mood and cognition is well documented in literature.

Nootropics or microbial modulators?

Randomized Controlled Trial > Medicine (Baltimore). 2019 Sep;98(37):e17186.
doi: 10.1097/MD.0000000000017186.

An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study

Adrian L Lopresti [1] [2], Stephen J Smith [1] [2], Hakeemudin Malvi [3], Rahul Kodgule [4]

Conclusions: These findings suggest that ashwagandha's stress-relieving effects may occur via its moderating effect on the hypothalamus-pituitary-adrenal axis. However, further investigation utilizing larger sample sizes, diverse clinical and cultural populations, and varying treatment dosages are needed to substantiate these findings.

Randomized Controlled Trial > J Prev Alzheimers Dis. 2017;4(1):12-15.
doi: 10.14283/jpad.2016.10.

Short-Term Impact of a Combined Nutraceutical on Cognitive Function, Perceived Stress and Depression in Young Elderly with Cognitive Impairment: A Pilot, Double-Blind, Randomized Clinical Trial

A F Cicero [1], M Bove, A Colletti, M Rizzo, F Fogacci, M Giovannini, C Borghi

Conclusions: We obtained a good and significant improvement of the cognitive functions tested with the MMSE, PSQ-Index and SRDS score, after 2 months of combined therapy of nutraceuticals. Further confirmation will be needed to verify these observations on the middle and long term in a larger number of subjects.

Randomized Controlled Trial > Food Funct. 2019 Jul 17;10(7):4423-4431.
doi: 10.1039/c9fo00913b.

Effect of Montmorency tart cherry juice on cognitive performance in older adults: a randomized controlled trial

Sheau C Chai [1], Jessica Jerusik [1], Kristina Davis [1], Regina S Wright [2], Zugui Zhang [3]

The within-group analysis showed that the visual sustained attention ($p < 0.0001$) and spatial working memory ($p = 0.06$) improved after the 12-week consumption of tart cherry juice compared with corresponding baseline values. Daily tart cherry juice consumption may improve cognitive abilities. This may be through anti-oxidative and anti-inflammatory properties of tart cherry and its ability to lower BP. Further research is needed to confirm these findings.

The compounds present in these botanicals are being metabolised and amplified by the gut microbiota.

The changes in microbiota composition triggered by these botanicals may be mediating positive mental health and neuroprotective outcomes.

PLOS ONE

Example: Ashwagandha

16S rRNA gene profiling and genome reconstruction reveal community metabolic interactions and prebiotic potential of medicinal herbs used in neurodegenerative disease and as nootropics

Christine Tara Peterson, Vandana Sharma, Stanislav N. Iablokov, Levent Albayrak, Kamil Khanipov, Sasha Uchitel, Deepak Chopra, Paul J. Mills, Yuriy Fofanov, Dmitry A. Rodionov, Scott N. Peterson

Nervine medicinal herbs alter fecal microbiota

Each medicinal herb promoted unique and strong alterations in microbial communities compared to control fecal cultures that provide amino acids but no carbohydrate energy source. PERMANOVA analysis (Bray Curtis) was used to identify the significance of the differences in community composition observed. All herb cultures were significantly different than control cultures ($p<0.01$–0.002). Each herb-supplemented culture was significantly different than all others ($p<0.04$–0.002), with three exceptions. Communities generated in Ashwagandha, Bacopa and Gotu Kola were not significantly different with respect to each other.

RepSeqSpecies	Level	Glucose	Galactose	Glucuronate	Galacturonat	Xylose	Arabinose	Rhamnose	Mannose	sum	Ashwagandha_FC	Bacopa_FC	Gotu Kola_
Cloacibacillus evryensis	F	0.33	0	0.33	0.33	0	0	0	0	0.99	4.338339048		
Alistipes putredinis	S	0	0	0	0	0	0	0	0	0	0.020026702		
Desulfovibrio desulfuricans	S	0	0	0	0	0	0	0	0	0	0.140210001		
Desulfovibrio piger	S	0	0	0	0	0	0	0	0	0	0.448092205		
Desulfovibrio simplex	G	0	0	0	0	0	0	0	0	0	0.02233581		
Eggerthella lenta	S	0	0	0	0	0	0	0	0	0	0.008042343		
Emergencia timonensis	S	0	0	0	0	0	0	0	0	0	0.951727489		
Flavonifractor plautii	S	0	0	0	0	0	0	0	0	0	0.016025832		
Ihubacter massiliensis	F	0	0	0	0	0	0	0	0	0	0.016025832		
Phascolarctobacterium fae	G	0	0	0	0	0	0	0	0	0	0.247890243		
Phocea massiliensis	S	0	0	0	0	0	0	0	0	0	1.331693029		

The medicinal herbs analyzed here are reported to alter host signaling *via* the gut-immune-brain axis [43–49]. A growing number of studies have linked the gut microbiota as a factor in the gut-brain axis [50–55]. It is intriguing to speculate that the gut microbiota modulatory capacity of these medicinal herbs may contribute to their therapeutic effect. This may occur as the result of herb catabolism that increases the bioactivity and/or bioabsorption of medicinal herbs. The bacterial metabolites produced by herb-selected communities may also alter gut and systemic immune functions. We expect that future and ongoing human interventions evaluating these herbs and their effects on gut microbiota will differ in many respects with the data reported here; however, our data suggest that medicinal herbs are potentially potent prebiotics that modulate a number of species with the potential to alter host physiology, particularly immune function. Our findings emphasize the potential relevance of gut microbiota as a factor in the mechanism of action of medicinal herbs. Additional studies involving healthy and individuals with neurodegenerative disease that include analysis of gut microbial communities and the microbially generated metabolites that gain access to the circulatory system will be of interest to improve our understanding of the variables that may positively or negatively influence the therapeutic efficacy of nervine medicinal herbs.

Examples currently under investigation

Review > Crit Rev Food Sci Nutr. 2020;60(4):597-625.
doi: 10.1080/10408398.2018.1546668. Epub 2019 Jan 7.

A critical review on grape polyphenols for neuroprotection: Strategies to enhance bioefficacy

Danyue Zhao [1], James E Simon [1], Qingli Wu [1]

Synergistic applications of encapsulation techniques (for physiochemical protection and bypassing xenobiotic metabolism) and dietary intervention strategies involving modulation of gut microbiota (for generating more bioavailable phenolic metabolites) appear promising, and may substantially enhance the bioefficacy, especially the neuroprotective efficacy, of orally consumed GPPs.

> Curr Dev Nutr. 2020 Nov 25;4(11):nzaa165. doi: 10.1093/cdn/nzaa165.
eCollection 2020 Nov.

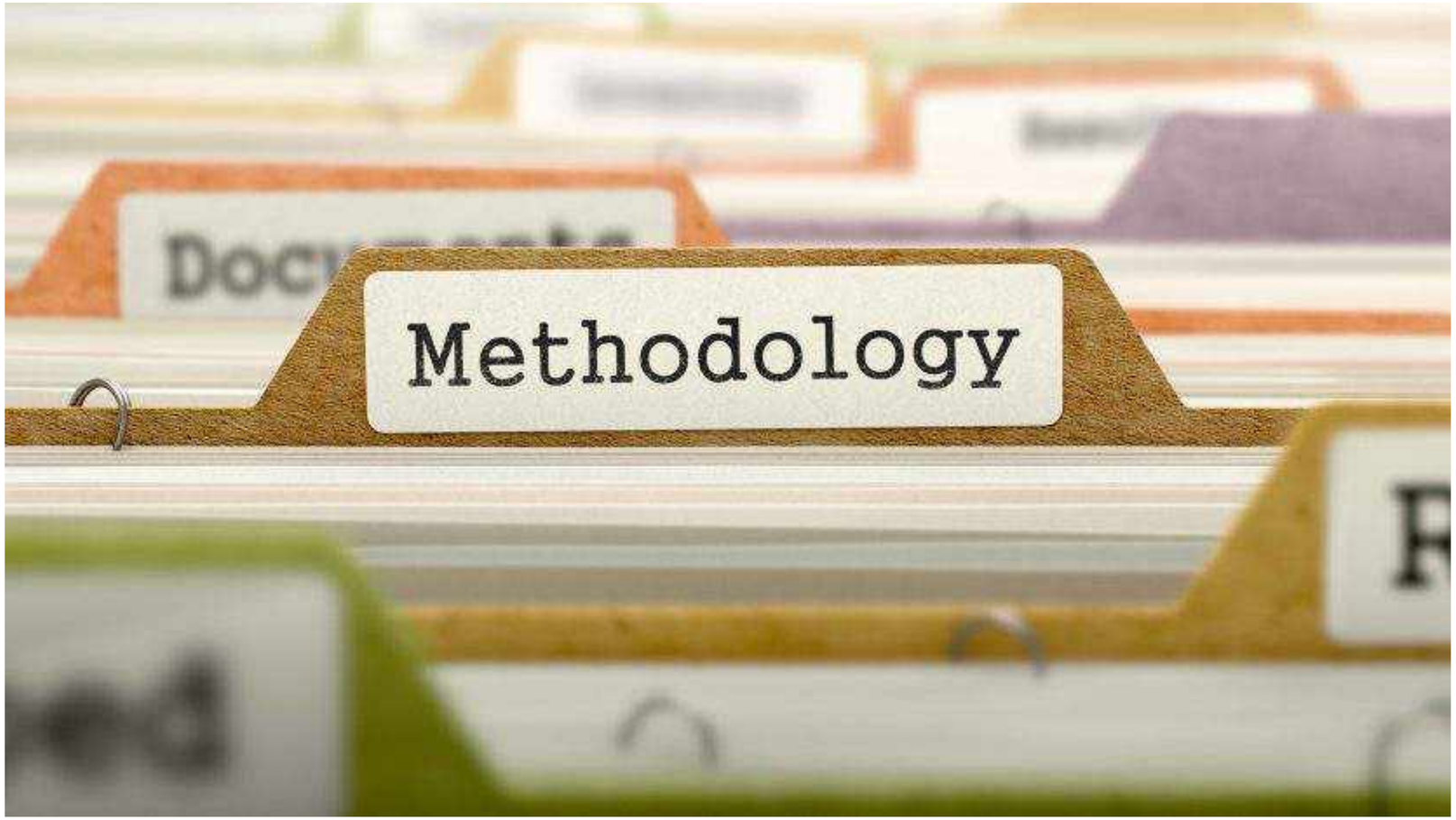
Pomegranate Metabolites Impact Tryptophan Metabolism in Humans and Mice

Jieping Yang [1], Yuanqiang Guo [2], Rupo Lee [1], Susanne M Henning [1], Jing Wang [1], Yajing Pan [3], Tianyu Qing [3], Mark Hsu [1], Alex Nguyen [1], Siddarth Prabha [4], Rashi Ojha [4], Gary W Small [4], David Heber [1], Zhaoping Li [1]

Background: We showed that pomegranate juice (PomJ) can help to maintain memory in adults aged >50 y. The mechanism for this effect is unknown, but might involve Trp and its metabolites, which are important in brain function.

The abundance of 2 genera, *Shigella* and *Catenibacterium*, was reduced by PomJ in humans as well as by UA in mice, and their abundance was negatively associated with blood IPA in humans and mice ($P < 0.05$).

Methodological considerations



Comorbidities

A simple PubMed search for “depression or anxiety” and “probiotics” confirms the limited number of randomised clinical trials where the primary outcomes are neuropsychiatric or neurodegenerative, i.e. most cohorts include individuals with co-morbidities, the most usual being:

- Irritable Bowel Syndrome (IBS)
- Obesity
- Pregnancy / lactation

Other questions to ponder

Attempting to measure changes in neuropsychiatric or neurodegenerative outcomes within cohorts that may have their own microbial signatures poses a challenge in itself. For example, would product **A** have the same antidepressant effect on obese versus non obese individuals? And would product **B** have the same anxiolytic effect in IBS vs non IBS patients?

PSYCHOSOMATIC MEDICINE

ORIGINAL ARTICLES

A Microbial Signature of Psychological Distress in Irritable Bowel Syndrome

Peter, Johannes MSc; Fournier, Camille MD; Durdevic, Marija MSc; Knoblich, Lukas MD; Keip, Bettina MSc; Dejaco, Clemens MD; Trauner, Michael MD; Moser, Gabriele MD **Author Information**

Psychosomatic Medicine: October 2018 - Volume 80 - Issue 8 - p 698-709
doi: 10.1097/PSY.0000000000000630

- Study aimed at exploring the microbial correlates of psychological distress in patients with IBS (Rome III criteria)

Interesting points:

- Study based on **n=48** IBS patients (**35 female**), average age 42
- Faecal samples underwent microbial 16S rRNA analyses

PSYCHOSOMATIC MEDICINE

ORIGINAL ARTICLES

A Microbial Signature of Psychological Distress in Irritable Bowel Syndrome

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- Depression was negatively associated with Lachnospiraceae abundance.
- Patients with anxiety were characterised by elevated Bacteroidaceae.
- Patients exceeding thresholds of distress, anxiety, depression, and stress perception showed significantly higher abundance of Proteobacteria.
- Diversity between patients with and without elevated stress, anxiety or depression was also compared, as well as the different IBS subtypes and severity, but there were no significant differences among any of the subgroups.

What about endotoxins, intestinal permeability and mood disorders

Brain, Behavior, and Immunity
Volume 48, August 2015, Pages 186-194

- The Enterobacteriaceae family includes inflammogenic enteric pathogens such as Hafnia *alvei*, Pseudomonas *aeruginosa*, Morganella *morganii*, Proteus *mirabilis*, Pseudomonas *putida*, Citrobacter *koseri* and Klebsiella *pneumonia.*
- All of these gram-negative bacteria are observed in normal gut flora but pose a problem when their abundance increases due to their ability to produce lipopolysaccharide (LPS).
- LPS is known to contribute to increased permeability of the gut wall in depressed patients. This may allow invasive gram negative bacteria to translocate into mesenteric lymph nodes or the systemic circulation.

Brain Behav Immun. 2015 Aug;48:186-94. doi: 10.1016/j.bbi.2015.03.016

Examples of LPS producers

Bilophila

Type:	Proteobacteria
Class:	Deltaproteobacteria
Order:	Desulfovibrionales
Family:	Desulfovibrionaceae
Genus:	Bilophila

Campylobacter

Type:	Epsilonbacteraeota
Class:	Campylobacteria
Order:	Campylobacterales
Family:	Campylobacteraceae
Genus:	Campylobacter

Citrobacter

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	Citrobacter

Enterobacter

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	Enterobacter

Klebsiella

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	Klebsiella

Pseudomonas

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Pseudomonadales
Family:	Pseudomonadaceae
Genus:	Pseudomonas

Escherichia-Shigella

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	Escherichia-Shigella

Sphingomonas

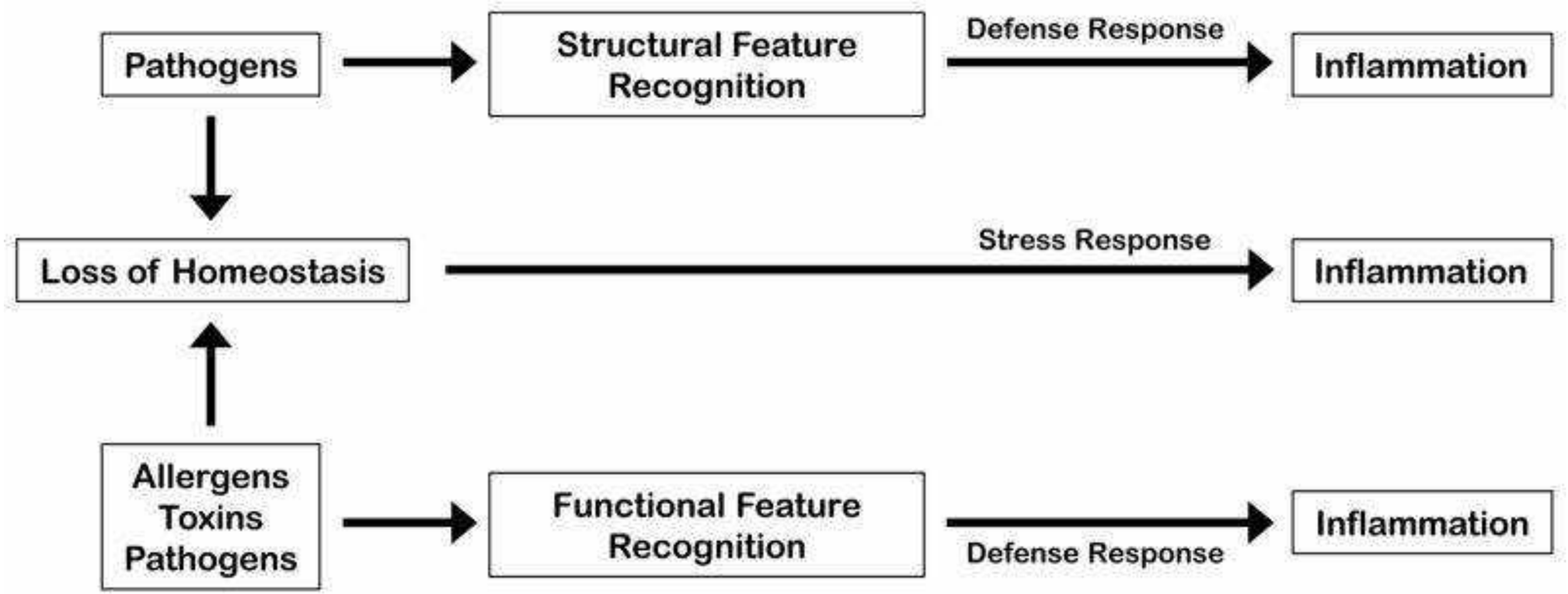
Type:	Proteobacteria
Class:	Alphaproteobacteria
Order:	Sphingomonadales
Family:	Sphingomonadaceae
Genus:	Sphingomonas

Salmonella

Type:	Proteobacteria
Class:	Gammaproteobacteria
Order:	Enterobacteriales
Family:	Enterobacteriaceae
Genus:	Salmonella

Molecular Cell

Pathogenic microbes and inflammation

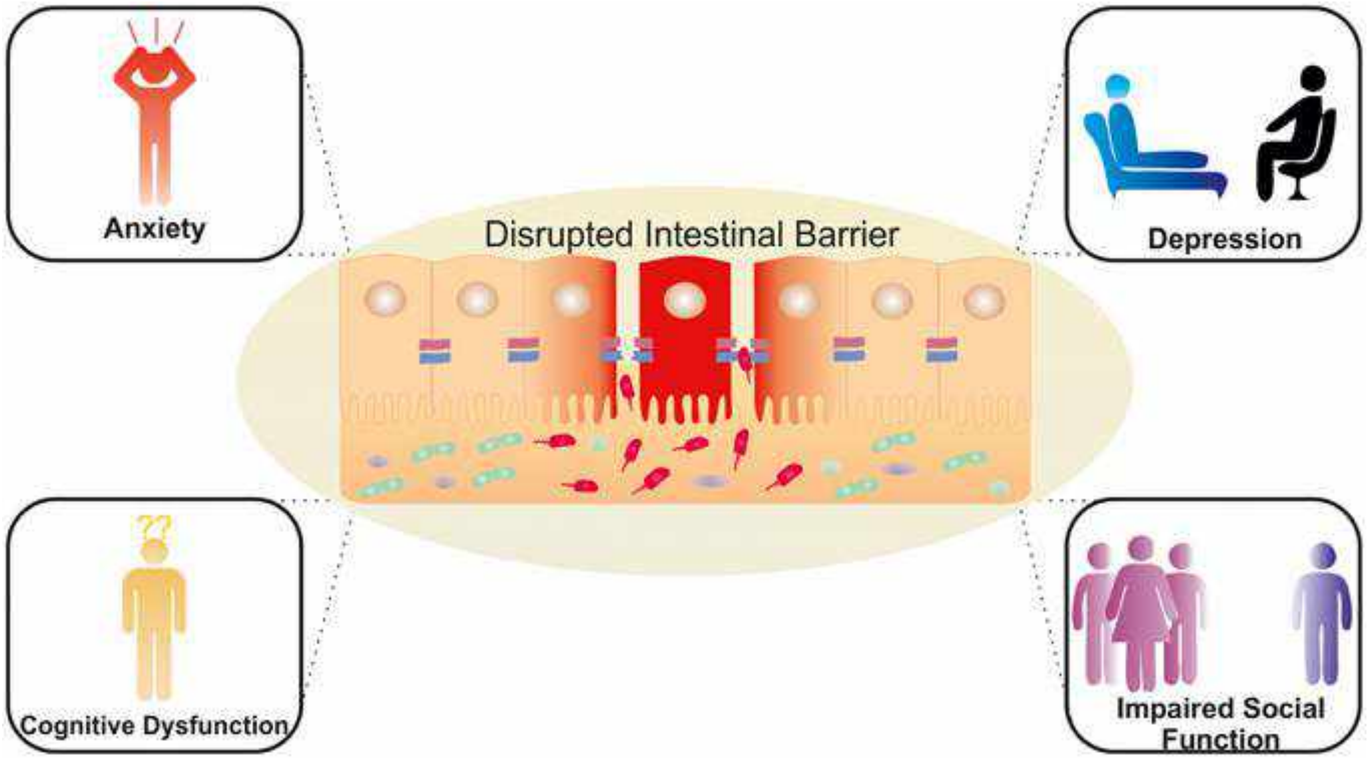


Mol Cell. 2014;54(2):281-288. doi:10.1016/j.molcel.2014.03.030

frontiers in Cellular Neuroscience

Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders

John R. Kelly[1,2], Paul J. Kennedy[1], John F. Cryan[1,3], Timothy G. Dinan[1,2], Gerard Clarke[1,2*] and Niall P. Hyland[1,4]



Intestinal permeability, the state that describes a disrupted intestinal barrier, is now an accepted mediator in the pathogenesis of neuropsychiatric and neurodegenerative disorders.

Front Cell Neurosci. 2015 Oct 14;9:392. doi: 10.3389/fncel.2015.00392

Is there a microbial signatures for anxiety and mild cognitive impairment (MCI)?

More difficult to ascertain but several studies identify:

- Lower abundance of Lactobacillus
- Lower abundance of butyrate producers,
  e.g. Faecalobacterium and Roseburia.

Physiol Rev. 2019 Oct 1;99(4):1877-2013. doi: 10.1152/physrev.00018.2018.

Nutrients. 2020 May 19;12(5):1468. doi: 10.3390/nu12051468

Would you supplement?

Progress in Neuro-Psychopharmacology and Biological Psychiatry
Available online 5 December 2020, 110189
In Press, Corrected Proof

Effects of probiotics supplementation on dementia and cognitive impairment: A systematic review and meta-analysis of preclinical and clinical studies

Cristofer Ruiz-Gonzalez [a], Pablo Roman [a, b, c], Lola Rueda-Ruzafa [d], Miguel Rodriguez-Arrastia [e, f], Diana Cardona [a, b]

- Inflammation of the central nervous system is associated with cognitive decline.
- Probiotic supplementation improved memory, cognitive function, biochemical and histological measures in subjects with dementia and cognitive impairment.

Interesting points:

- A total of 16 articles (10 preclinical and 6 clinical) that met the inclusion criteria for the systematic review, and 15 articles (10 preclinical and 5 clinical) for meta-analysis.
- Mini-Mental State Examination (MMSE), Repeatable Battery for the Assessment of Neurophychological Status (RBANS) and Test Your Memory (TYM) tests used to assess cognitive function.

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What is the onset time for these interventions to cause an effect?

Reference	Country	Participants (PG/CG)	Probiotic	Intervention characteristics	Variables	Tools	Results
Agahi et al. (2018)	Iran	**AD patients** 25/23	*Lactobacillus fermentum, plantarum and acidophilus Bifidobacterium lactis, bifidum and longum* Capsules	12 weeks 3×10^9 CFU	Orientation, recognition, calculation, verbal fluency, similarity, naming, memory, visuospatial and copying skills	TYM	**PG** ↑TYM score (14.64/17.42) **CG** ↑TYM score (14.35/17.47) $p = 0.82$
Akbari et al. (2016)	Iran	**AD patients** 30/30	*Lactobacillus acidophilus, casei and fermentum Bifidobacterium bififidum* Milk	12 weeks 200 ml/day 2×10^9 CFU/g for each	Cognitive function: attention, orientation, memory, recall, calculation, language and drawing	MMSE	**PG** ↑ MMSE score (+27.90% ± 8.07) **CG** ↓ MMSE score (-5.03% ± 3.00) $p < .001$

Progress in Neuro-Psychopharmacology and Biological Psychiatry
Available online 5 December 2020, 110189
In Press, Corrected Proof

Table 3
Characteristics of clinical studies (n = 6).

Reference	Country	Participants (PG/CG)	Probiotic	Intervention characteristics	Variables	Tools	Results
Xiao et al. (2020)	Japan	**MCI subjects** PG = 40 CG = 39	*Bifidobacterium Breve* A1 Capsules	16 weeks 2×10^{10} CFU	Immediate memory Visuospatial memory Language Attention Delayed memory	RBANS JMCIS	**PG**: ↑ RBANS score, ↑ JMCIS score; **CG**: ↑ RBANS score ($p < .0001$), ↓ JMCIS score ($p = .052$)
Tamtaji et al. (2019)	Iran	**AD patients** Se G. = 26 Se + P G. = 27C.G. = 30	*Lactobacillus acidophilus* *Lactobacillus casei* *Bifidubacterium bifidum* Capsules	12 weeks 2×10^{9} CFU	Cognitive function	MMSE	**Se+ P G.**: ↑ MMSE; **CG**: ↓ MMSE; **Se G**: ↑ MMSE ($p < .001$)
Hwang et al. (2019)	Korea	**MCI subjects** 50/50	Mixture of fermented soybean and *Lactobacillus plantarum* C-29 Capsules	12 weeks 1×10^{10} CFU	Attention Working memory Verbal memory Neurotrophins	ACPT DST VLT ELISA	**PG**: ↑ Attention ($p = .02$), ↑ Working memory ($p < .05$), ↑ Verbal memory, ↑ Combined cognitive function, ↑ BDNF ($p = .007$); **CG**: No changes in BDNF levels ($p = 0.15$)
Kobayashi et al. (2019)	Japan	**MCI subjects** 59/58	*Bifidobacterium Breve* A1 Capsules	12 weeks 2×10^{10} CFU	Memory, visuospatial capacity, language and attention Cognitive function	RBANS MMSE	**PG**: ↑ RBANS score (+5.27), ↑ Language ($p < .001$), ↑ Attention ($p < .001$), ↑ MMSE score ($p < .001$) (+1.63); **CG**: ↑ RBANS score ($p = 0.87$) (+4.65), ↑ Language ($p < .05$), ↑ Attention, ↑ MMSE score ($p = 0.62$) ($p < .001$) (+1.76)

Most studies don't report interim onset, but a before / after measure and comparison.

JOURNAL OF ALZHEIMER'S DISEASE

Probiotic Bifidobacterium breve in Improving Cognitive Functions of Older Adults with Suspected Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial

Jinzhong Xiao [1], Noriko Katsumata [1], Francois Bernier [1], Kazuya Ohno [1], Yuki Yamauchi [1], Toshitaka Odamaki [1], Kenji Yoshikawa [2], Kumie Ito [3], Toshiyuki Kaneko [4]

- 80 healthy older adults suffering from MCI were divided into two even groups to receive once daily either probiotic (B. breve A1, 2×10^{10} CFU) or placebo for 16 weeks.
- Significant improvement in domain scores of immediate memory, visuospatial/constructional, and delayed memory.
- Study results indicate B. breve A1 is a safe and effective approach for improving memory functions of suspected MCI subjects.

Interesting point:

- Cognitive functions were assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Japanese version of the MCI Screen (JMCIS) tests before and after the study as primary and secondary endpoints, respectively.

J Alzheimers Dis. 2020;77(1):139-147. doi: 10.3233/JAD-200488

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Example of how most studies don't report interim onset, but a before / after measure and comparison.

However, it is advantageous to know how long a product might take to have an effect, so it is worth thinking of including interim measures, both biological, i.e. a microbiome test, as well as self reported outcomes.

Table 2

Results of the neuropsychological tests (ITT)

	Baseline		16 weeks			
	Placebo	Probiotic	Placebo	Probiotic	Difference (95% CI)	*p*
RBANS total score	32.4 (7.5)	30.5 (10.6)	38.3 (13.0)	47.9 (13.4)	11.3 (6.7 to 15.8)	<0.0001
Immediate memory	36.4 (8.4)	36.9 (10.5)	38.7 (9.9)	48.2 (11.2)	9.2 (5.1 to 13.3)	<0.0001
Visuospatial/Constructional	34.4 (14.4)	32.1 (13.2)	35.8 (13.5)	46.2 (10.0)	11.4 (6.8 to 16.0)	<0.0001
Language	47.3 (7.8)	49.9 (10.7)	50.1 (8.8)	54.2 (8.1)	3.5 (–0.2 to 7.2)	0.064
Attention	49.2 (10.0)	45.7 (11.0)	53.3 (11.8)	51.1 (10.2)	0.5 (–2.7 to 3.8)	0.74
Delayed memory	31.1 (12.3)	31.1 (12.0)	34.6 (13.5)	45.6 (14.2)	11.0 (6.6 to 15.3)	<0.0001
JMCIS score	63.2 (7.5)	61.3 (9.2)	60.5 (9.9)	62.6 (8.4)	3.5 (0.2 to 6.9)	0.052

Baseline (Placebo: n=40, Probiotic: n=40), 16 weeks (Placebo: n=39, Probiotic: n=40). Values are indicated as mean (SD). Differences are indicated by changes of LSM between Placebo and Probiotice at 16 weeks. Effect of Probiotic was indicated in intergroup difference (95% CI) and p value by ANCOVA in intention-to-treat (ITT) analysis. RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; JMCIS, The Japanese version of the MCI Screen.

J Alzheimers Dis. 2020;77(1):139-147. doi: 10.3233/JAD-200488

Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment – a meta-analysis of randomized controlled trials

Haoyue Den [1], Xunhu Dong [2], Mingliang Chen [2] [3], Zhongmin Zou [2]

- 5 studies involving 297 subjects met eligibility. There was a significant improvement in cognition, while a significant reduction in **malondialdehyde** and high-sensitivity **C-reactive** protein post-intervention levels between the probiotics and control groups.
- Probiotics improved cognitive performance in AD or MCI patients, possibly through decreasing levels of inflammatory and oxidative biomarkers.
- However, current evidence is insufficient, and more reliable evidence from large-scale, long-period, RCT is needed.

Interesting points:

- Analysis of **malondialdehyde** as a biomarker of oxidative stress, and HS-CRP as a marker of systemic inflammation can provide powerful insights on the effects of interventions with probiotic products.

Aging (Albany NY). 2020 Feb 15;12(4):4010-4039. doi: 10.18632/aging.102810

Key points

Probiotic supplementation could provide an adequate therapeutic strategy for a range of mood and cognitive disorders, based on clinical and preclinical evidence. In the absence of approved legal health claims, translating preclinical data into clinical recommendations and listening to the individual / client / patient becomes essential.

Phytonutrients such as polyphenols from dietary and botanical sources are emerging as potentially powerful modulators of brain health through via the gut microbiota. This is a novel research avenue that warrants thorough investigation.