The Role of the Gut and Oral Microbiome in Brain Health

Mechanisms, Evidence, and Clinical Implications

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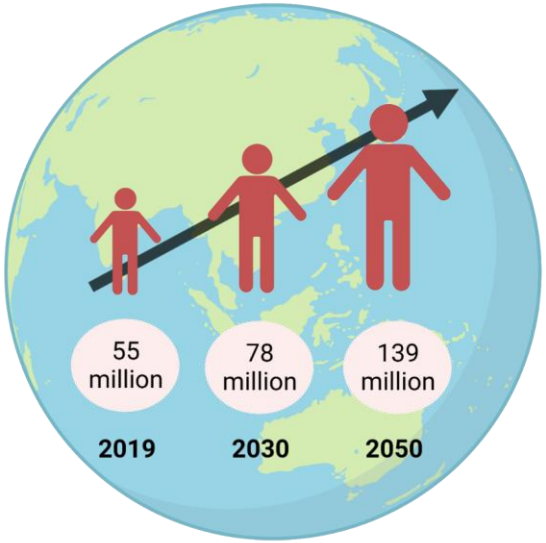
Athena SWAN Silver Award

Ageing population… Ageing brains…

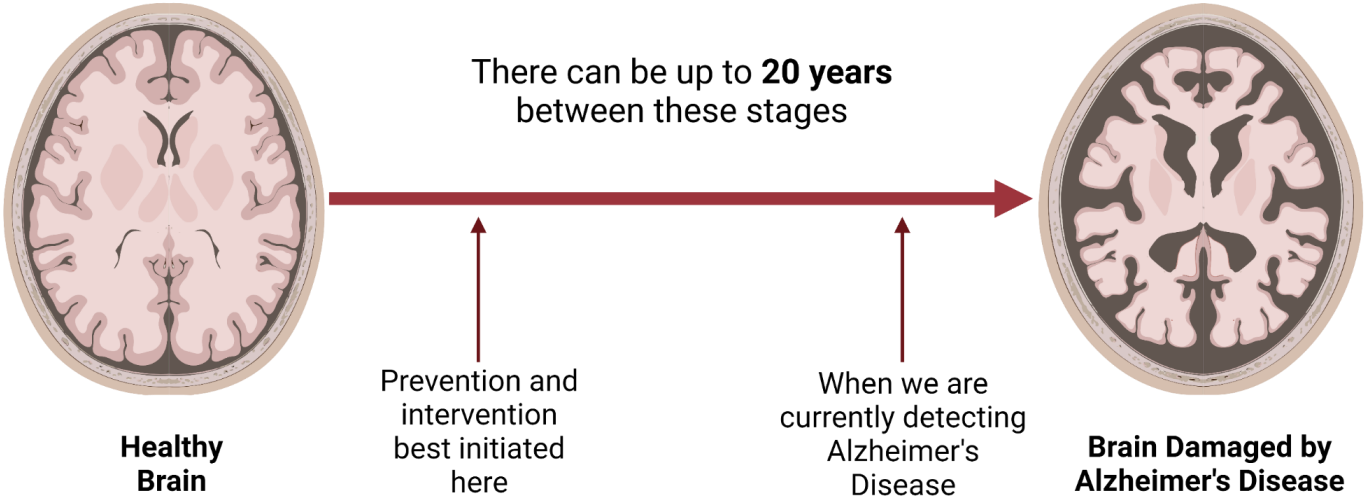
1 in 6 people in the world will be aged 60 years by 2030 and is projected to rise dramatically from 1 billion in 2020 to 2.1 billion by 2050 (WHO 2024)

Over 55 million people live with dementia worldwide today and this number is projected to increase to 139 million by 2050 (Alzheimer's Disease International, 2021)



Identifying those who are at risk for developing dementia may provide an opportunity for intervention. In the US, delaying the onset of Alzheimer's by five years could reduce the prevalence of the disease by 41% by 2050.

Age-related cognitive decline and dementia



Risk factors and brain vulnerability

Modifiable risk factors

- Unhealthy diet
- Physical inactivity
- Tobacco/alcohol/drugs
- Stress/anxiety
- Poor dental health
- Sleep

Intermediate risk factors

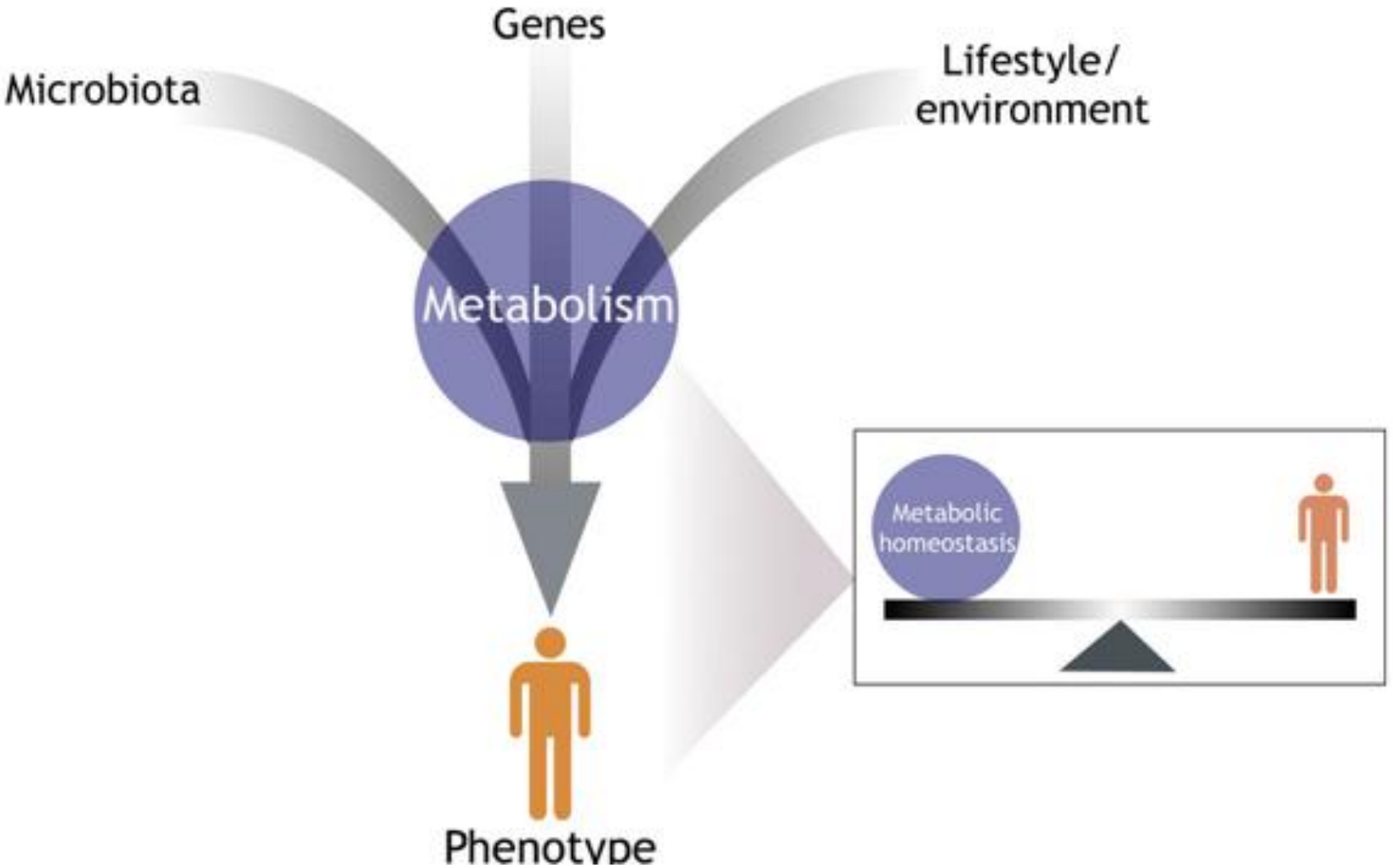
- Cardiovascular disease
- Obesity/Diabetes
- Pulmonary disease
- Mental Illness
- Hypertension
- Gut dysbiosis
- Periodontitis

Non modifiable risk factors

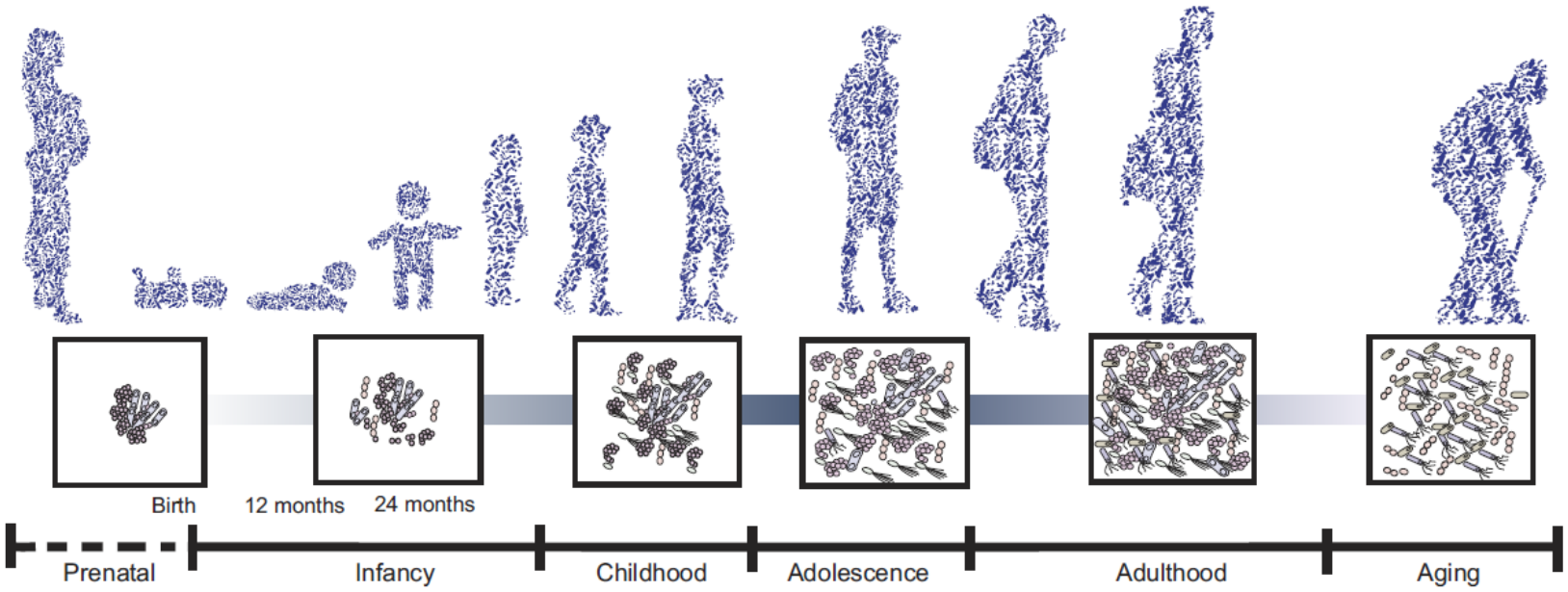
- Age
- Family history
- Genetics

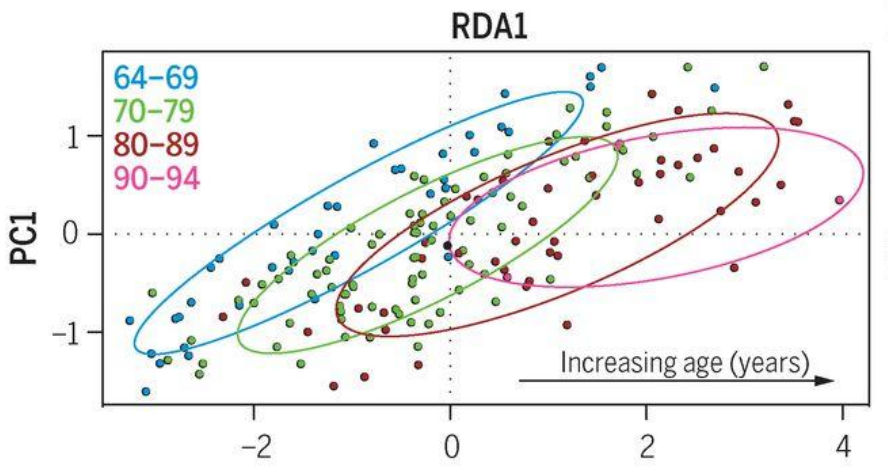
Vauzour D et al. Ageing Research Reviews. 2017, 35:222-240

Brain vulnerability: the role of the exposome



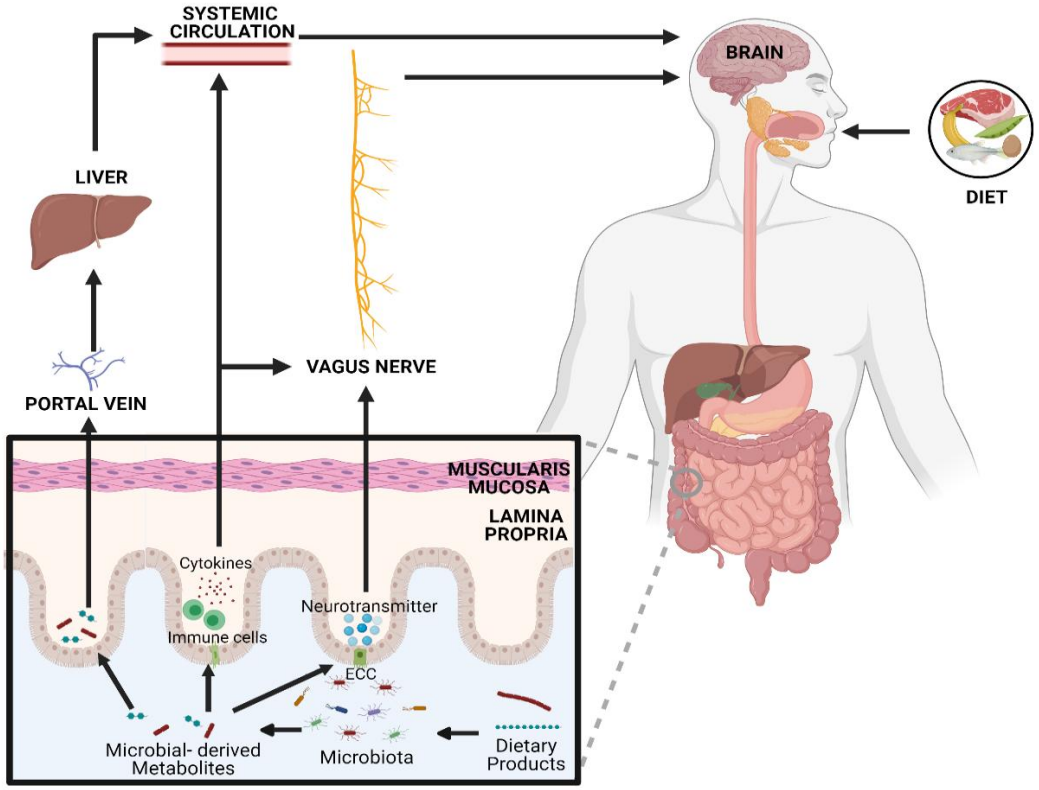
Our microbiome is changing as we age





O'Toole P and Jeffery I.B. Science (2015)

The brain and our body closely interact through the gut-brain axis



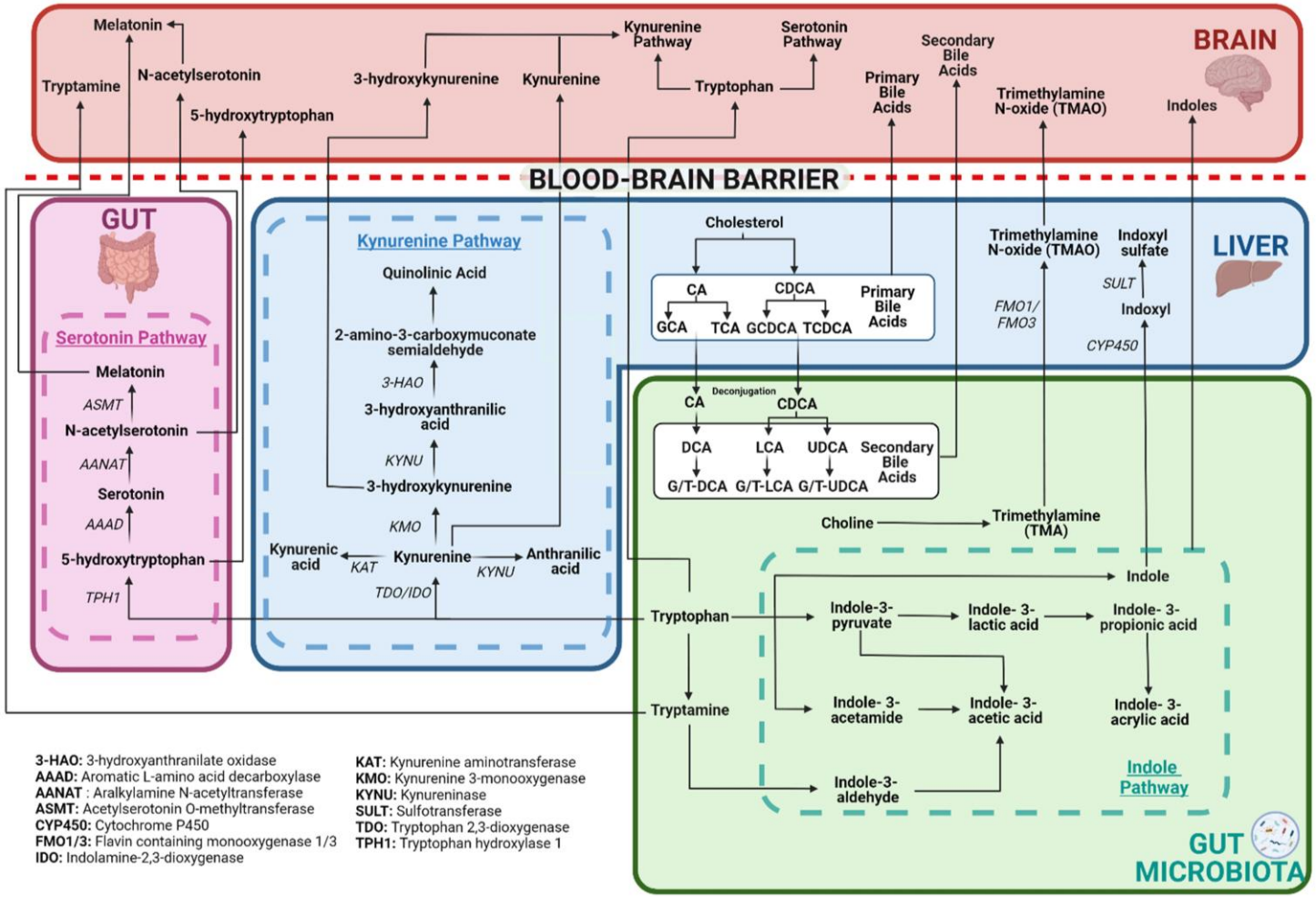
Connell et al. Mol Neurodegener (2022)

<u>3 Signalling Mechanisms of the Microbiota-Gut-Brain Axis:</u>

1. Neurocrine
   - Enteric Nervous System
   - Vagal afferents
2. Endocrine
   - Gut-Derived Metabolites
3. Immune Mediators
   - LPS
   - Cytokines
   - Microbe-Associated Molecular Patterns (MAMPs)

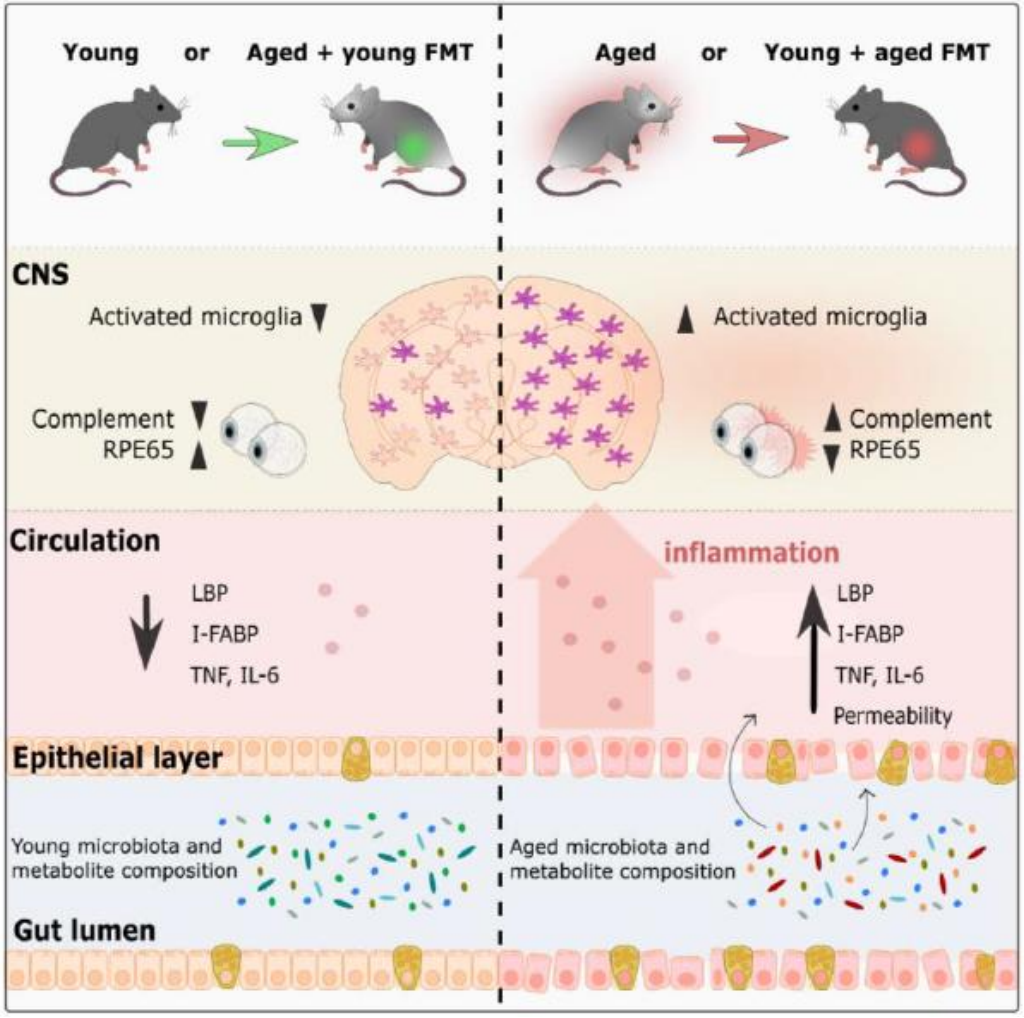
Chakrabarti A et al. Cell Mol Life Sci. (2022)

Microbial-derived metabolites and the brain



Connell et al. Mol Neurodegener (2022)

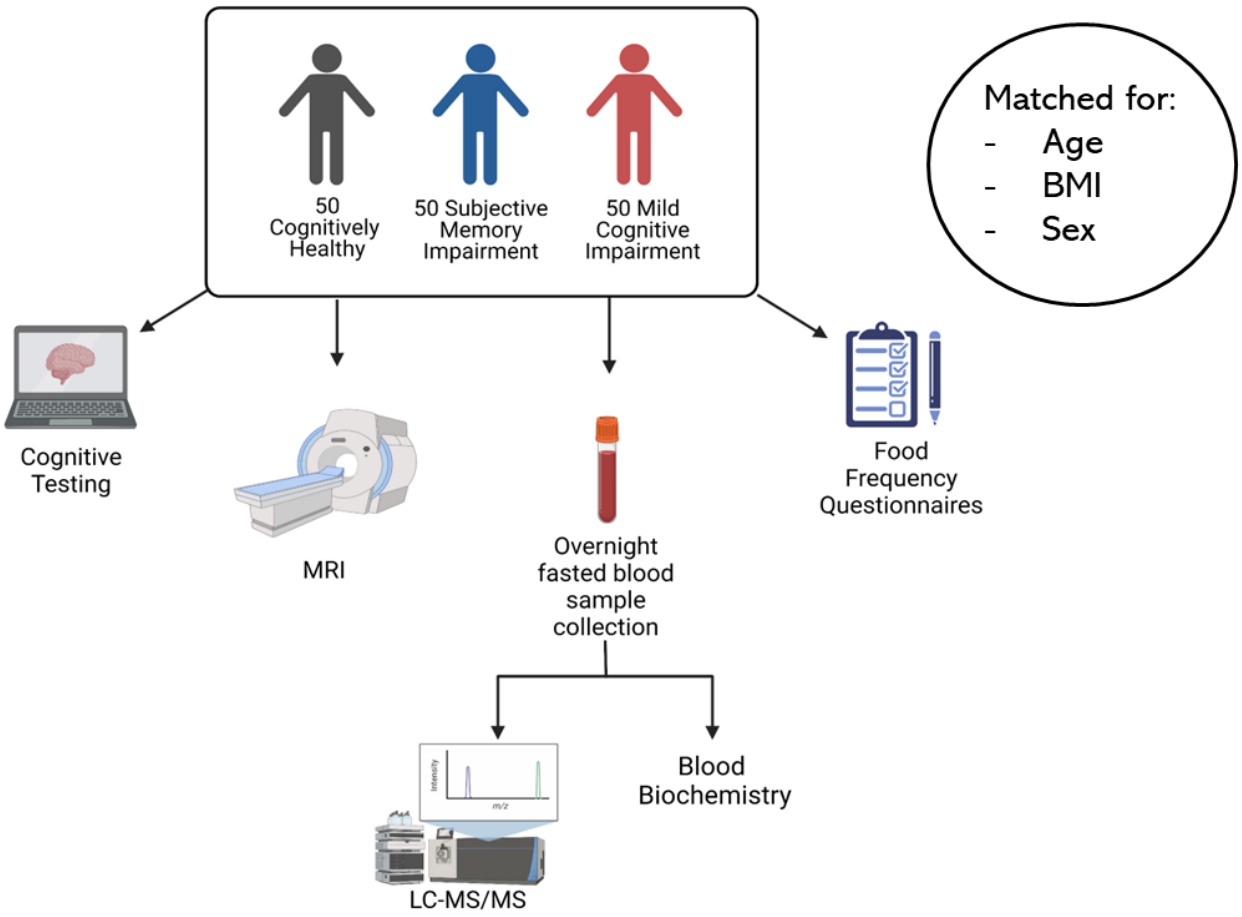
Faecal microbiota transfer reverses hallmarks of the ageing gut, eye, and brain



D'Amato et al. Microbiome (2020) 8:140 Parker A et al. Microbiome (2022); 10(1):68

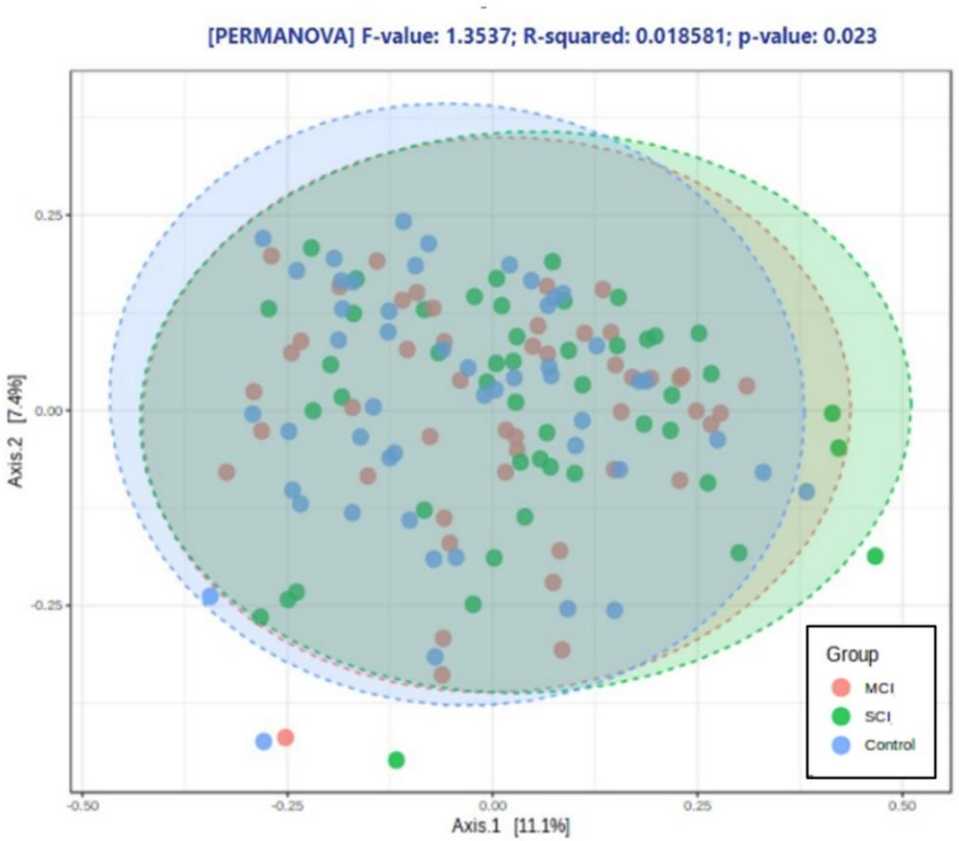
Dietary and microbe-derived metabolites as an early indicator of cognitive decline and dementia

- Use a targeted metabolomics approach to identify microbial-derived risk factors of early cognitive decline in human serum samples.
- Establish a predictive model via hypothesis-driven analysis, using machine learning algorithms.



Connell et al. Gut Microbes 2026

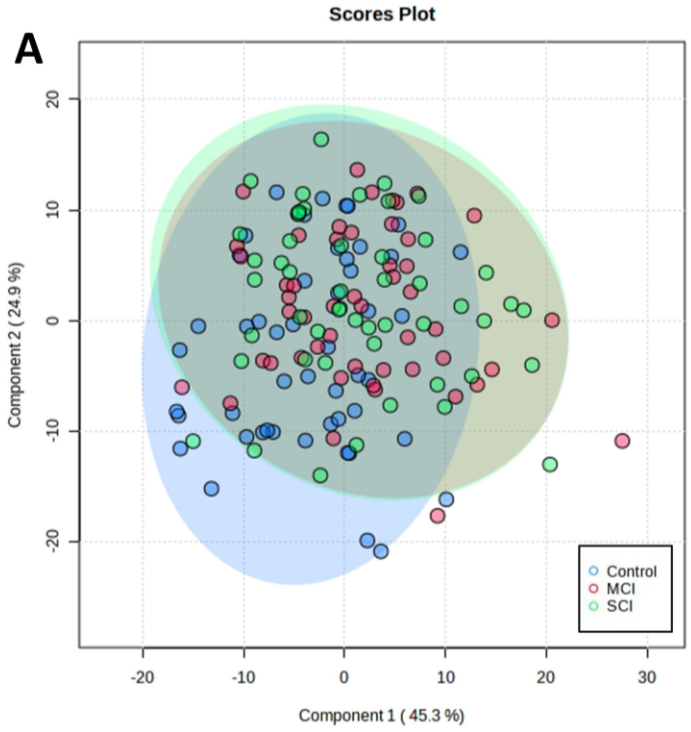
Microbiome β-diversity is significantly altered in early cognitive decline

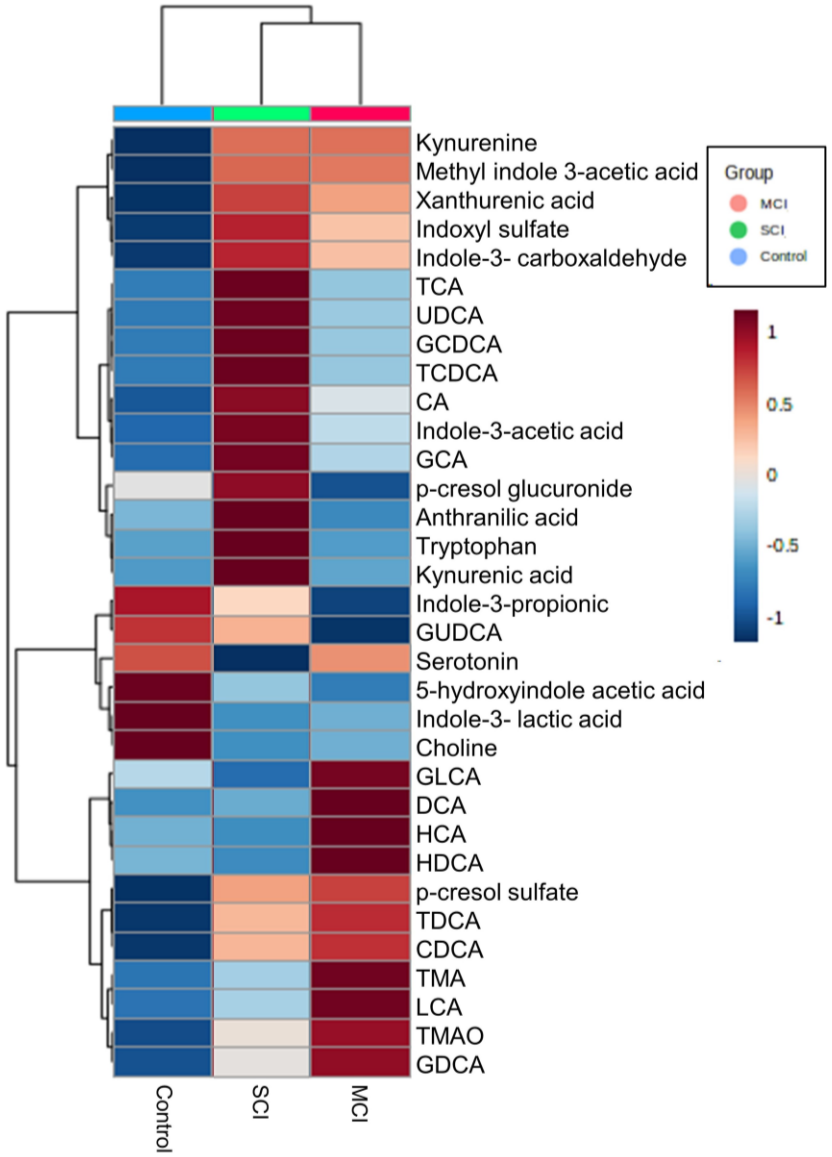


Pair	F-value	R-Squared	P-value	FDR
Control vs SCI	1.77	0.02	0.01 *	0.03 *
SCI vs MCI	1.02	0.01	0.38	0.38
MCI vs Control	1.26	0.01	0.10	0.15

Connell et al. Gut Microbes 2026

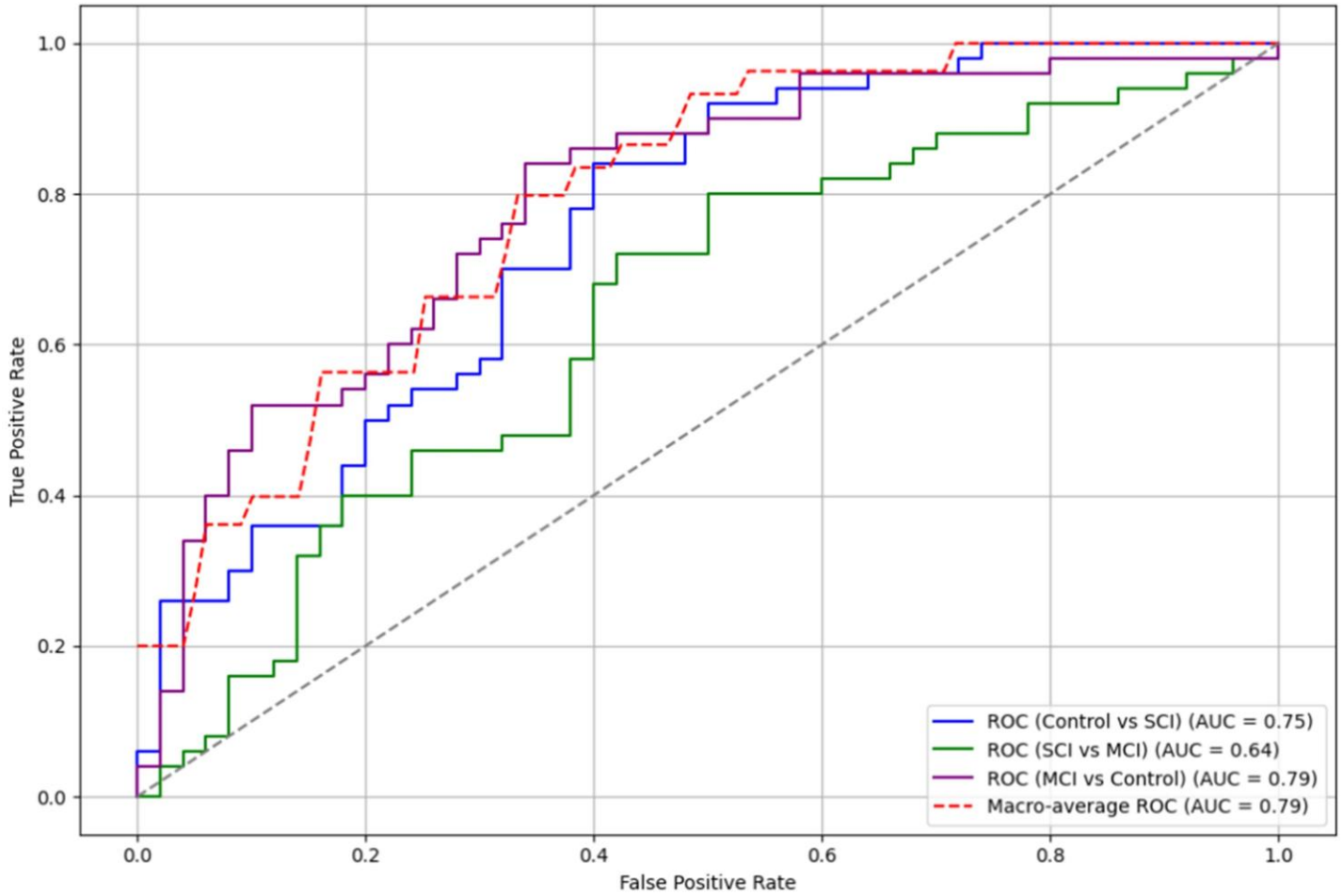
Metabolic shift occurs in early cognitive decline





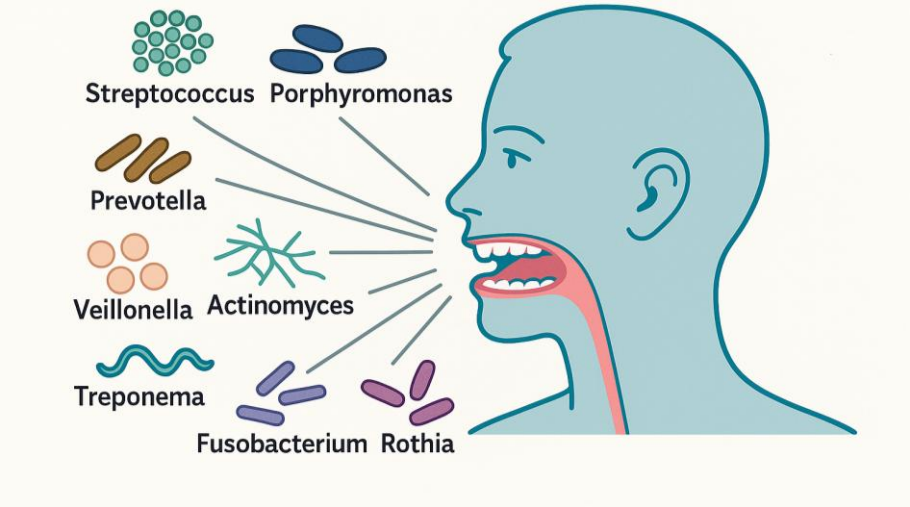
Connell et al. Gut Microbes 2026

Six gut and diet derived circulatory metabolites are predictive of preclinical AD



Connell et al. Gut Microbes 2026

Oral Microbiota: The Overlooked Player

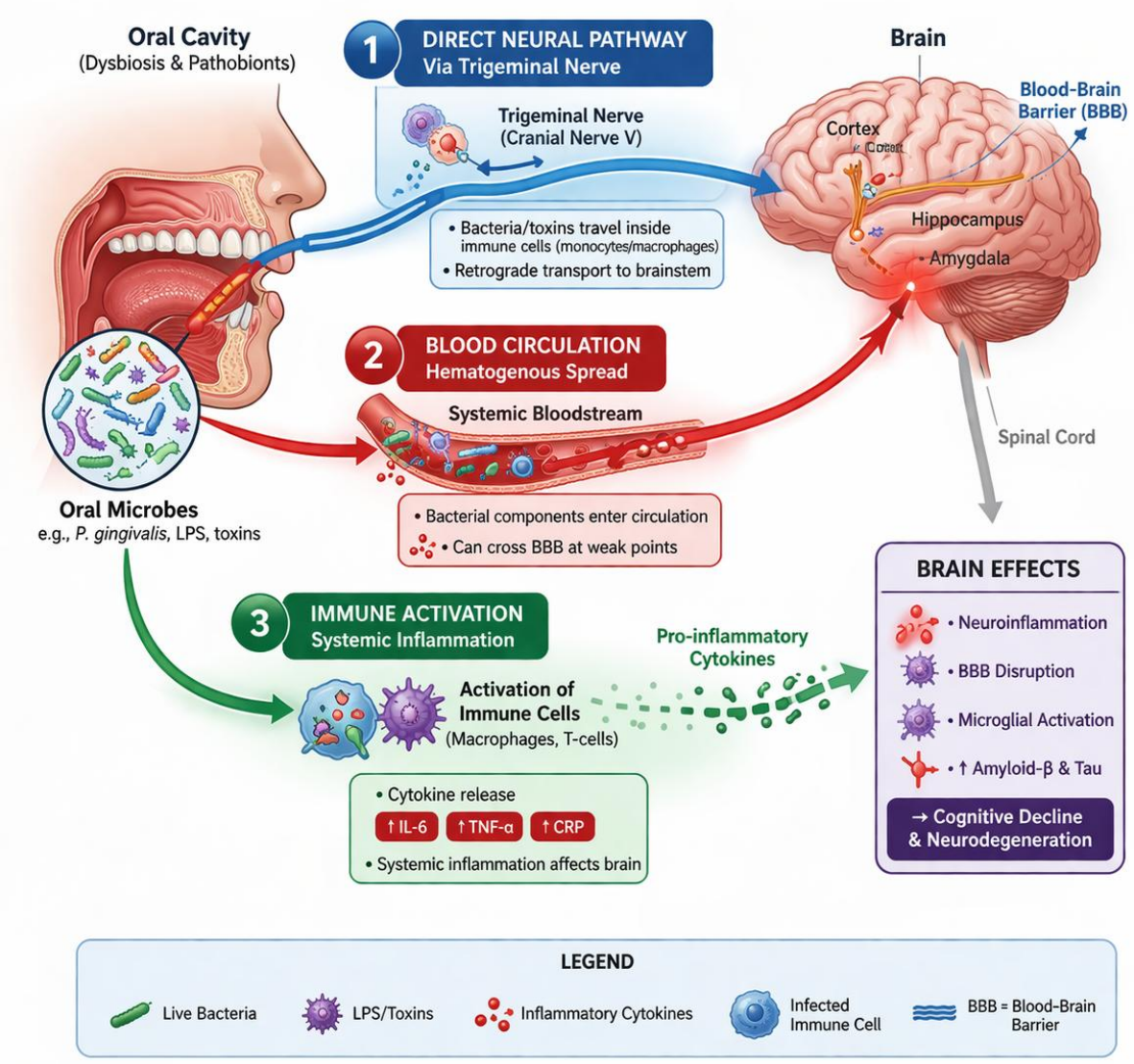


Second largest microbial community in the body (includes bacteria, fungi, viruses)

Periodontal disease is the 11th most prevalent condition in the world, with a prevalence ranging from 20 to 50% worldwide (Nazir M et al. Sci World J. 2020).

It is characterized by the inflammation of the periodontium, the specialized tissues that both surround and support the teeth

The Oral–Brain Axis: Pathways and mechanisms

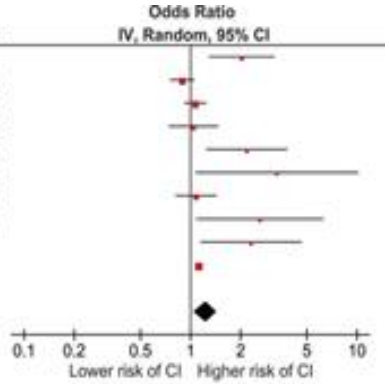


Poor periodontal health increase the risk of both cognitive decline and dementia

Cognitive decline

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Shimazaki et al., (Pooled OR, tooth loss)	0.708	0.233	7.5%	2.03 [1.29, 3.20]	2001
Stewart et al., (PPD)	−0.113	0.087	17.0%	0.89 [0.75, 1.06]	2013
Tsakos et al., (0 teeth remaining)	0.067	0.078	17.7%	1.07 [0.92, 1.25]	2015
Okamoto et al., (PPD)	0.039	0.175	10.5%	1.04 [0.74, 1.47]	2015
Nilsson et al., (Alveolar bone loss)	0.779	0.287	5.6%	2.18 [1.24, 3.82]	2018
Saito et al., (0-9 teeth remaining)	1.196	0.575	1.8%	3.31 [1.07, 10.21]	2018
Hatta et al., (PPD)	0.077	0.146	12.4%	1.08 [0.81, 1.44]	2018
Iwasaki et al.,(Periodontitis)	0.959	0.449	2.7%	2.61 [1.08, 6.29]	2019
Bumb et al., (severe periodontitis)	0.837	0.358	4.0%	2.31 [1.14, 4.66]	2021
Xu et al., (Pooled rate of tooth loss)	0.113	0.027	20.8%	1.12 [1.06, 1.18]	2021
Total (95% CI)			**100.0%**	**1.23 [1.05, 1.44]**	

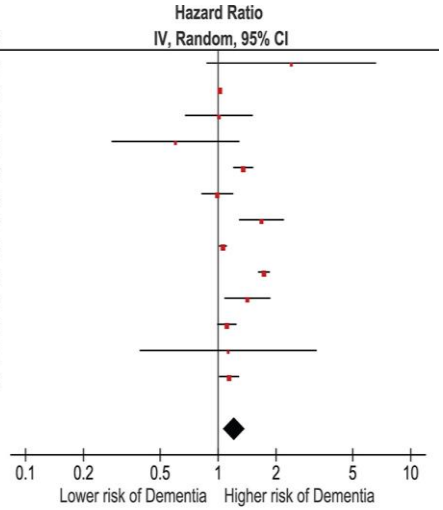
Heterogeneity: Tau² = 0.03; χ^2 = 30.38, df = 9 (p = 0.0004); I² = 70%
Test for overall effect: Z = 2.61 (p = 0.009)



Dementia

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Stein et al., (Alveolar bone loss)	0.875	0.517	1.4%	2.40 [0.87, 6.61]	2007
Paganini-Hill et al., (Pooled HR, tooth loss)	0.02	0.007	11.5%	1.02 [1.01, 1.03]	2012
Yamamoto et al., (≤19 teeth remaining)	0.009	0.207	5.3%	1.01 [0.67, 1.51]	2012
Arrive et al., (Pooled HR, PPD)	−0.51	0.39	2.2%	0.60 [0.28, 1.29]	2012
Batty et al., (Pooled HR, tooth loss)	0.3	0.061	10.5%	1.35 [1.20, 1.52]	2013
Hansson et al., (Pooled HR, tooth loss)	−0.01	0.097	9.2%	0.99 [0.82, 1.20]	2014
Takeuchi et al. (Pooled HR, tooth loss)	0.518	0.137	7.6%	1.68 [1.28, 2.20]	2017
Choi et al., (Periodontitis)	0.058	0.024	11.3%	1.06 [1.01, 1.11]	2019
Lee et al., (Periodontitis)	0.548	0.036	11.1%	1.73 [1.61, 1.86]	2020
Beydoun et al., (Pooled HR, PPD)	0.35	0.14	7.5%	1.42 [1.08, 1.87]	2020
Demmer et al., (Pooled HR, periodontitis)	0.104	0.059	10.5%	1.11 [0.99, 1.25]	2020
Holmer et al., (PPD)	0.12	0.54	1.3%	1.13 [0.39, 3.25]	2021
Kiuchi et al., (≤19 teeth remaining)	0.131	0.061	10.5%	1.14 [1.01, 1.28]	2022
Total (95% CI)			**100.0%**	**1.21 [1.07, 1.38]**	

Heterogeneity: Tau² = 0.04; χ^2 = 250.30, df = 12 (p < 0.00001); I² = 95%
Test for overall effect: Z = 2.97 (p = 0.003)



Asher et al. J American Geriatrics Society, 2022

Oral microbiome, *APOE4* genotype and cognitive impairment

PNAS NEXUS

PNAS Nexus, 2025, **4**, pgae543

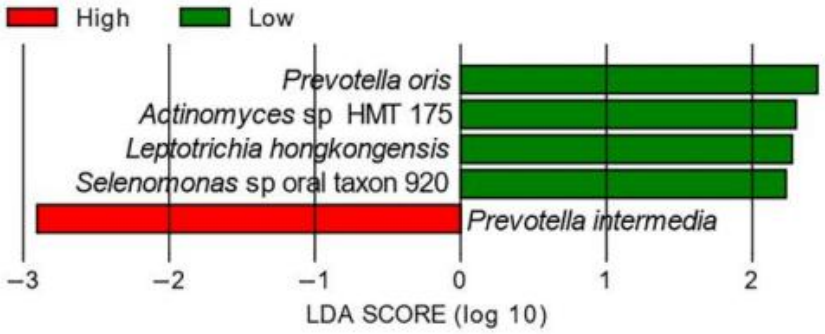
https://doi.org/10.1093/pnasnexus/pgae543

Advance access publication 28 January 2025

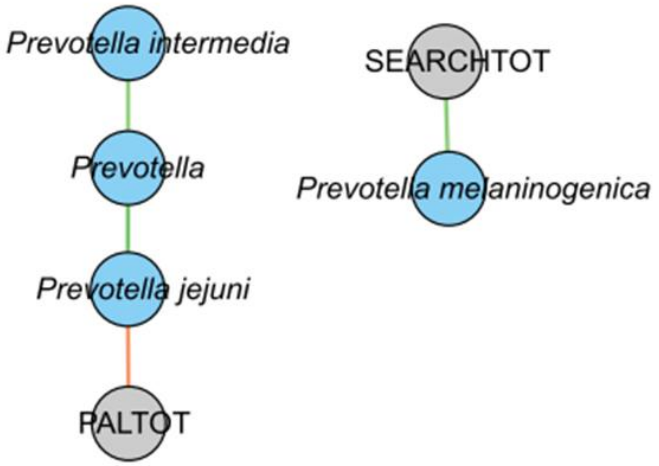
Research Report

Oral microbiome and nitric oxide biomarkers in older people with mild cognitive impairment and APOE4 genotype

Joanna E. L'Heureux[a], Anne Corbett[a], Clive Ballard[a], David Vauzour[b], Byron Creese[c], Paul G. Winyard[a], Andrew M. Jones[a] and Anni Vanhatalo[a,*]



Higher abundance of *P. intermedia* in *APOE4* carriers in the MCI group



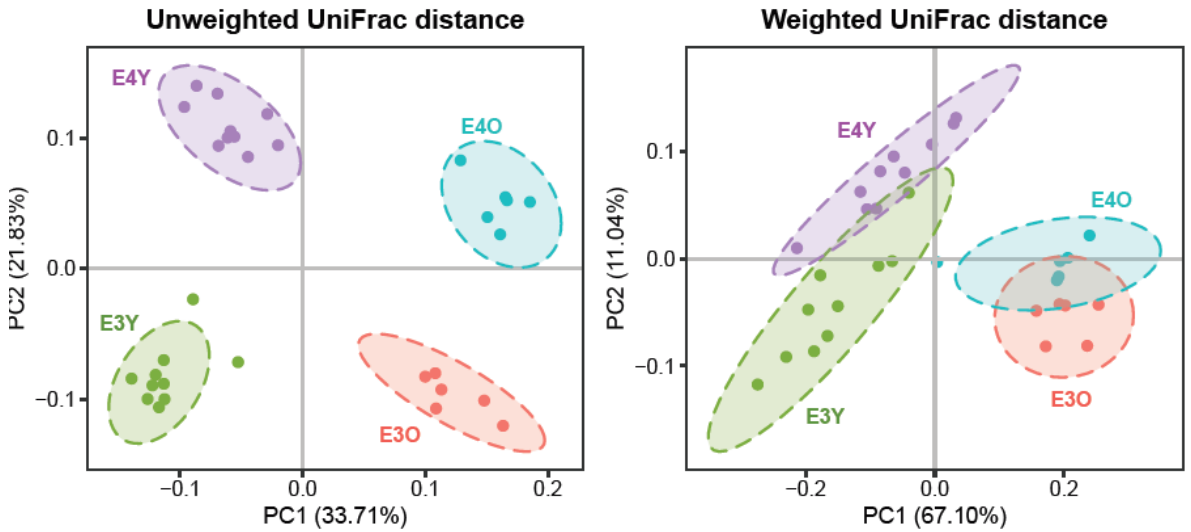
P. intermedia in *APOE4* carriers in the MCI group was negatively correlated with Paired Associate Learning (PAL), a measure of episodic memory

Impact of *APOE* genotype on the microbiome

The FASEB Journal

APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer's disease pathophysiology

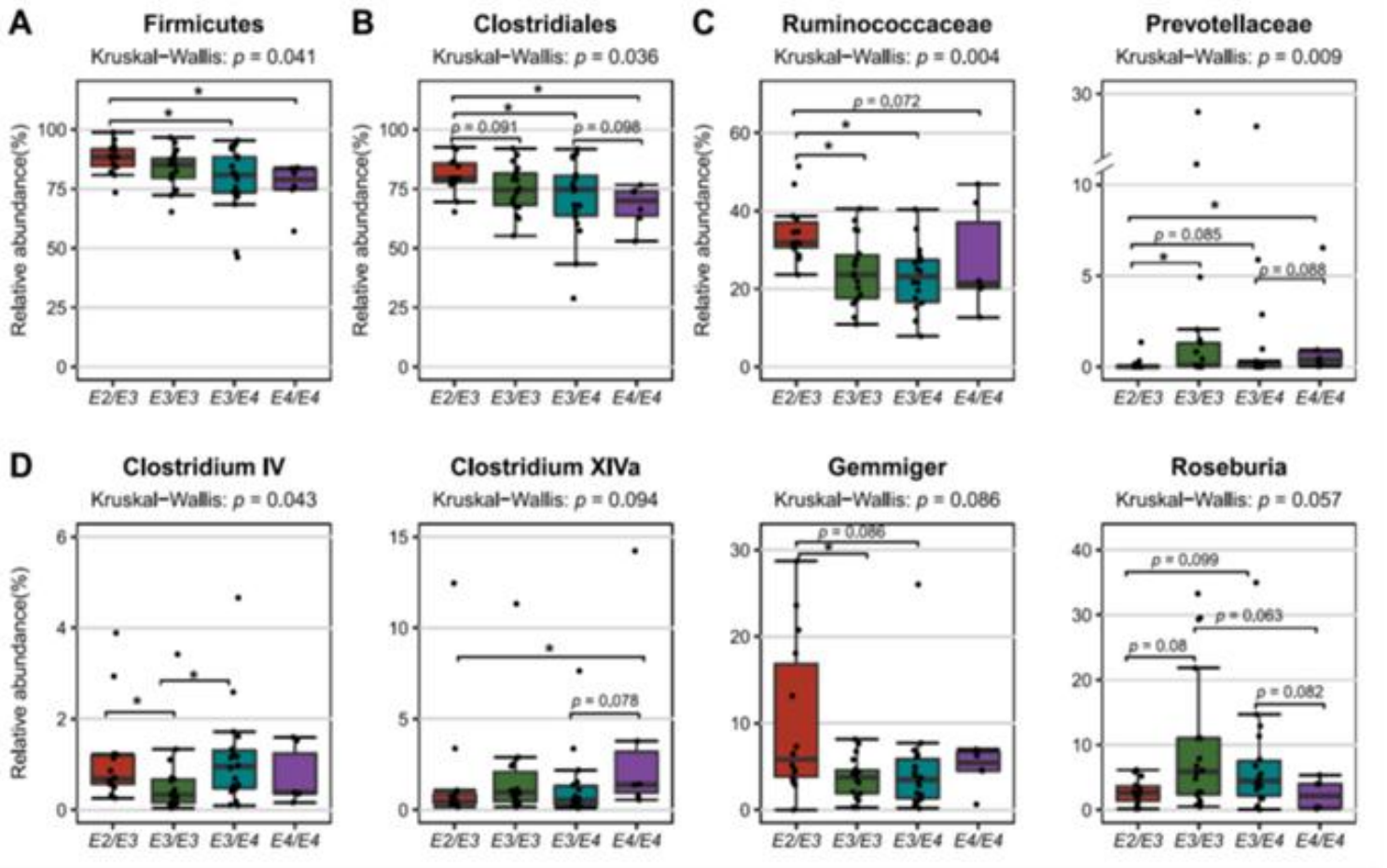
Tam T. T. Tran, Simone Corsini, Lee Kellingray, Claire Hegarty, Gwénaëlle Le Gall, Arjan Narbad, Michael Müller, Noemi Tejera, Paul W. O'Toole, Anne-Marie Minihane, David Vauzour



PERMANOVA tests	Unweighted UniFrac		Weighted UniFrac	
	R^2	*p*	R^2	*p*
Age: Young vs. Old	0.325	0.001	0.554	0.001
Young mice: E3Y vs. E4Y	0.473	0.001	0.345	0.002
Old mice: E3O vs. E4O	0.395	0.004	0.306	0.003
APOE genotype: E3 vs. E4	0.217	0.001	0.087	0.018
Age and *APOE* genotype	0.622	0.001	0.702	0.001

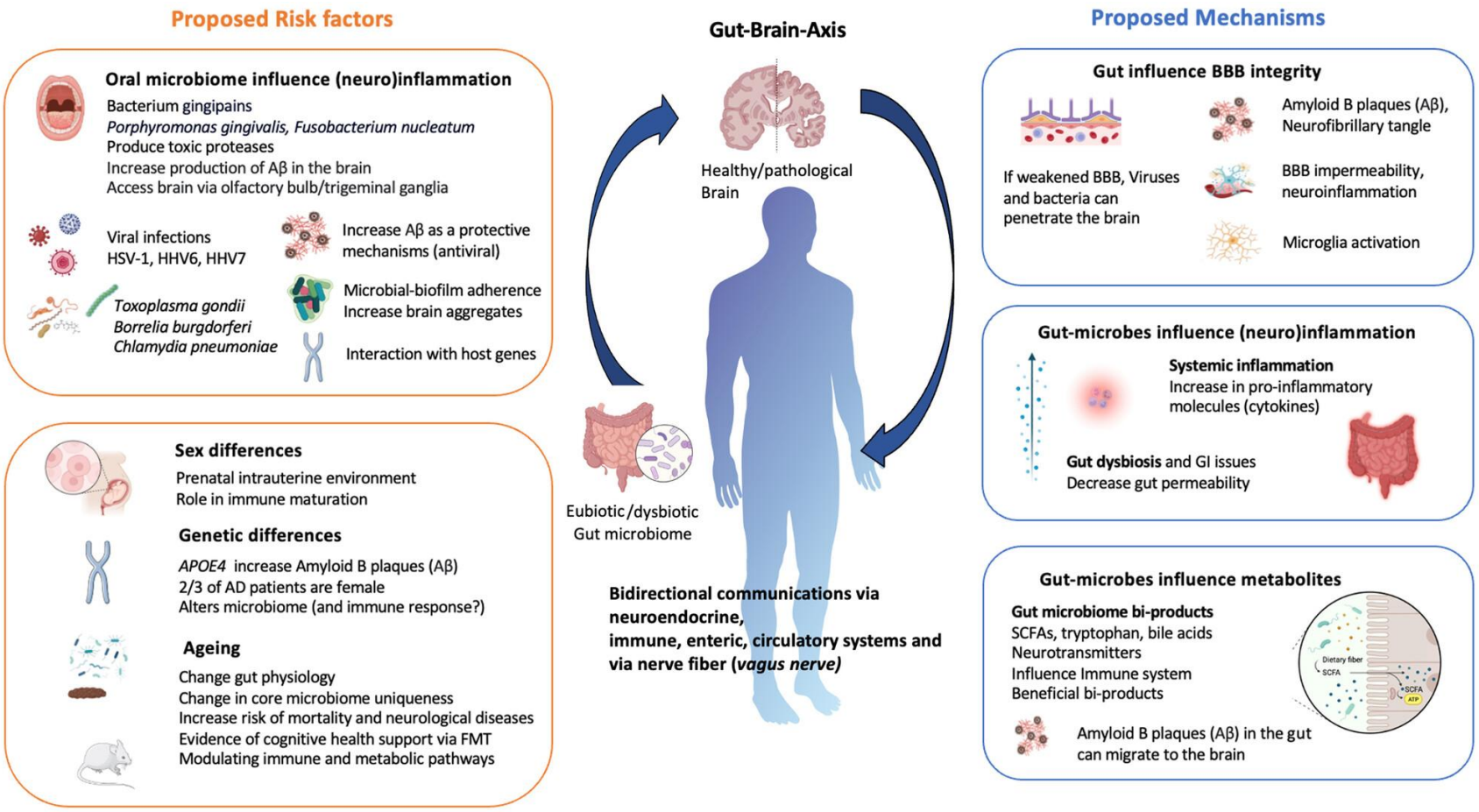
Tran TTT et al. FASEB J. 2019 Jul;33(7):8221-8231

APOE genotype shifts the human microbiome



Tran TTT et al. FASEB J. 2019 Jul;33(7):8221-8231

Summary



Williams, Z.A.P. et al. Microbial Biotechnology 2024

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