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U.S. Department
of Veterans Affairs

Small Microbes, Big Minds: The Gut's Connection to Brain Health

CU-CSU Summit, 13 Aug 26

Andrew Hoisington, PhD, PE



Disclaimer

Dr. Hoisington has no relevant financial interests to disclose

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VA Brain Health Coordinating Center



Dr. Lisa Brenner



Dr. David Cifu

BHCC Mission: Enhance VHA's Learning Health System by creating an integrated Brain Health Network facilitated by a Coordinating Center and Targeted Network Sites to promote clinical-research interactions in the area of Veteran Brain Health.

Anschutz Body, Brain Biome, and Behavior Health Laboratory

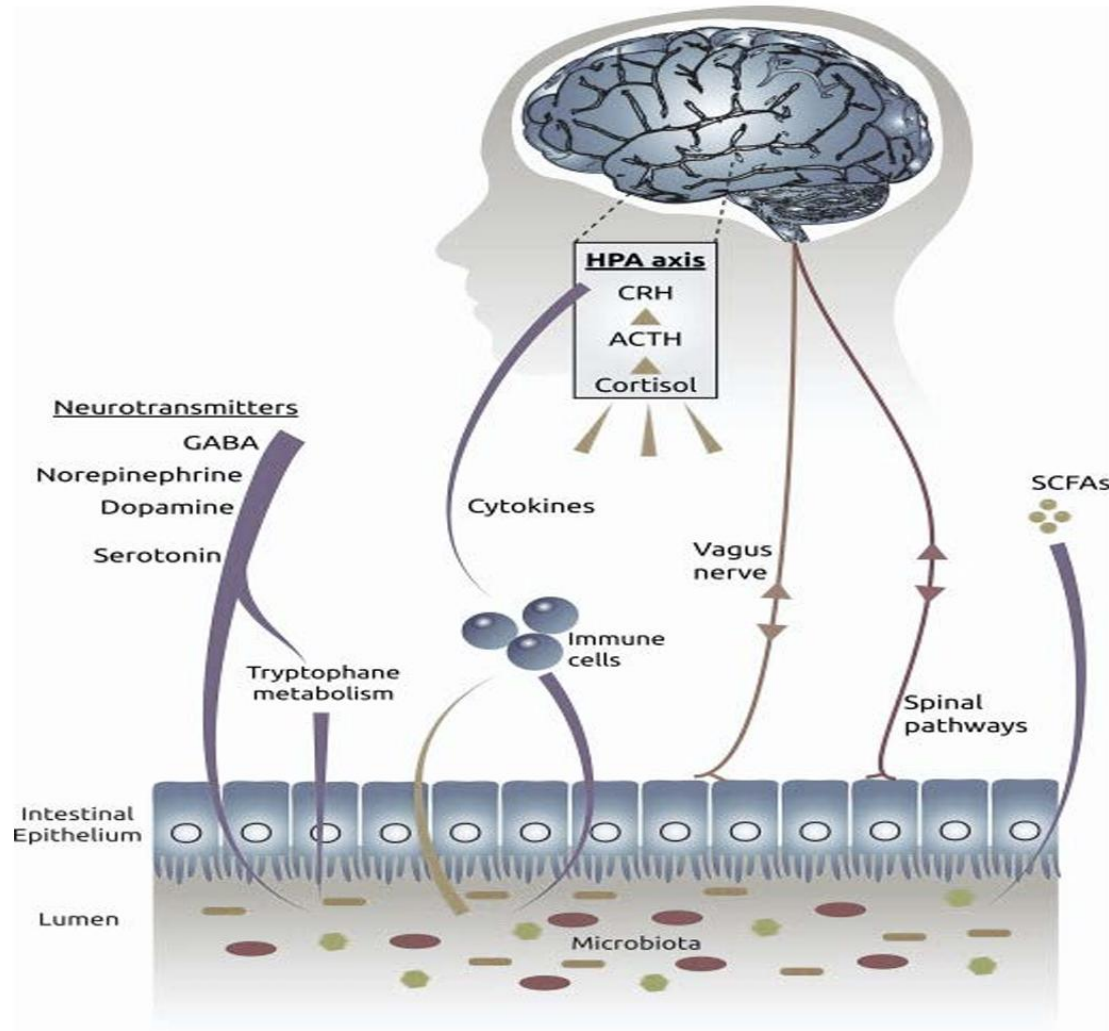


Dr. Lisa Brenner



Dr. Andrew Hoisington

B4 Health Mission: To focus on connections between the Brain, Body, Biome, and Behavior to enhance physical and mental health through investigation and education.



Dinan, Timothy G., and John F. Cryan. "The microbiome-gut-brain axis in health and disease." *Gastroenterology Clinics* 46.1 (2017): 77-89.

Gut dysbiosis impairs recovery after spinal cord injury

Kristina A. Kigerl,¹ Jodie C.E. Hall,¹ Lingling Wang,² Xiaokui Mo,³ Zhongtang Yu,² and Phillip G. Popovich¹

BRAIN
ORIGINAL ARTICLE



Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis

Stefanie Grabrucker,^{1,2,†} Moira Marizzoni,^{3,4,†} Edina Silajdžić,^{5,†} Nicola Lopizzo,^{3,6} Elisa Mombelli,³ Sarah Nicolas,^{1,2} Sebastian Dohm-Hansen,^{1,2,7} Catia Scassellati,³ Davide Vito Moretti,⁸ Melissa Rosa,³ Karina Hoffmann,⁵ John F. Cryan,^{1,2} Olivia F. O'Leary,^{1,2} Jane A. English,^{1,7} Aonghus Lavelle,^{1,2} Cora O'Neill,^{2,9} Sandrine Thuret,^{5,†} Annamaria Cattaneo^{3,6,†} and Yvonne M. Nolan^{1,2,†}

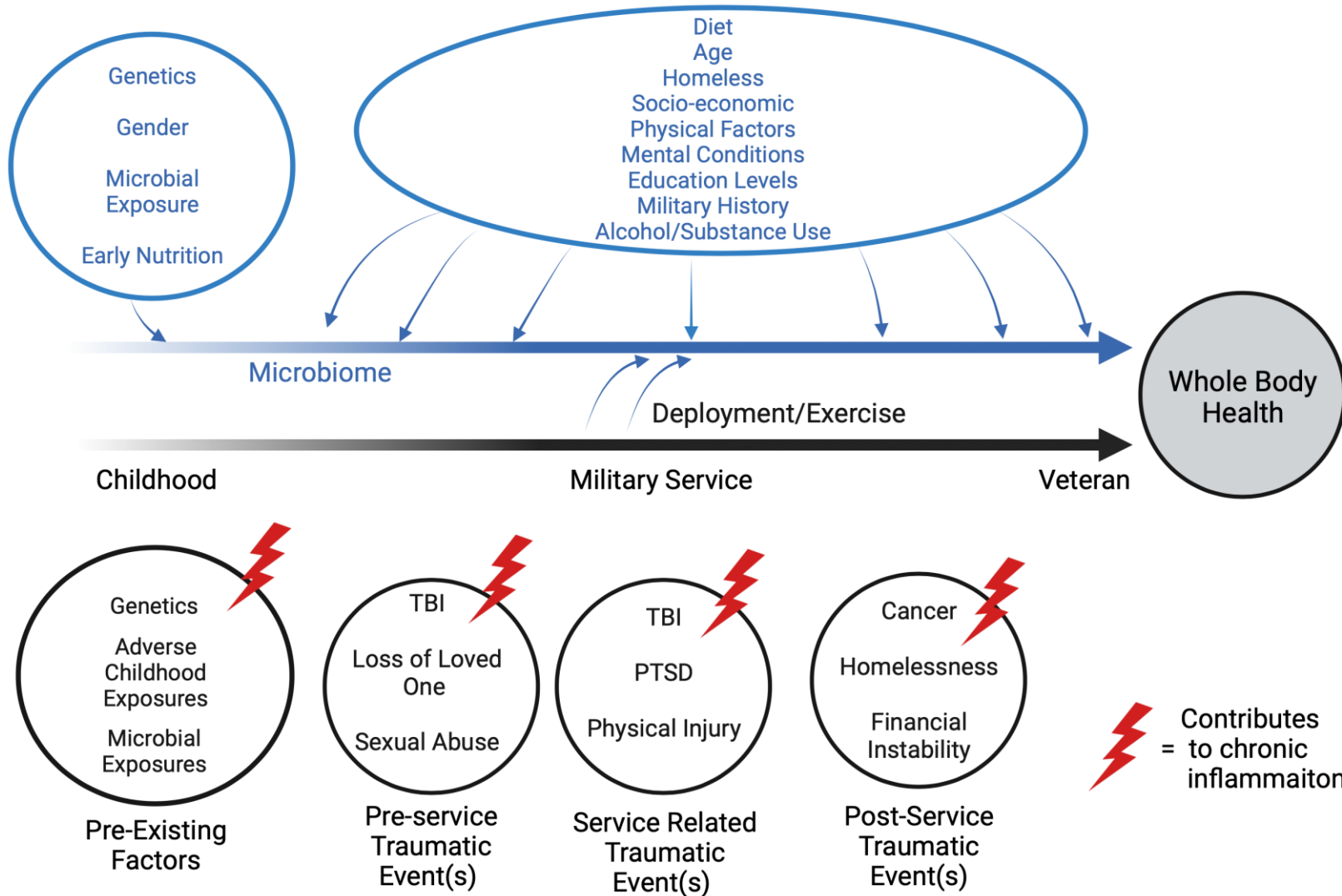
Journal of Alzheimer's Disease 78 (2020) 683–697
DOI 10.3233/JAD-200306
IOS Press

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Short-Chain Fatty Acids and Lipopolysaccharide as Mediators Between Gut Dysbiosis and Amyloid Pathology in Alzheimer's Disease

Moira Marizzoni^{a,b,1,*}, Annamaria Cattaneo^{b,1}, Peppino Mirabelli^c, Cristina Festari^a, Nicola Lopizzo^{b,d}, Valentina Nicolosi^a, Elisa Mombelli^b, Monica Mazzelli^b, Delia Luongo^e, Daniele Naviglio^f, Luigi Coppola^c, Marco Salvatore^e and Giovanni B. Frisoni^g

Theoretical Model – Life Cycle Approach



Risk Factors for Cognitive Decline

- Advanced Age
- Genetics (APOE ε4)
- Hypertension
- Diabetes
- Obesity
- High Cholesterol
- Chronic Stress
- Depression
- TBI
- Hearing/Vision Loss
- Physical Inactivity
- Poor Diet
- Smoking
- Social Isolation
- Sleep deprivation

Lifestyle for Brain Health (LIBRA): a new model for dementia prevention

Olga J. G. Schiepers¹, Sebastian Köhler¹, Kay Deckers¹, Kate Irving^{2,†}, Catherine A. O'Donnell³, Marjan van den Akker⁴, Frans R. J. Verhey¹, Stephanie J. B. Vos¹, Marjolein E. de Vugt¹ and Martin P. J. van Boxtel¹

Table 1 Algorithm for calculating individual Lifestyle for Brain Health (LIBRA) score^a

Modifiable risk factor	Relative risk (RR)	Ln (RR)/beta weight	Score	Available in MAAS
Low/moderate alcohol consumption	0.74	−0.30 (reference)	−1.0	+
Coronary heart disease	1.36	0.31	+1.0	+
Physical inactivity	1.39	0.33	+1.1	+
Renal dysfunction	1.39	0.33	+1.1	+
Diabetes	1.47	0.39	+1.3	+
High cholesterol	1.54	0.43	+1.4	+
Smoking	1.59	0.46	+1.5	+
Obesity	1.60	0.47	+1.6	+
Hypertension	1.61	0.48	+1.6	+
Mediterranean diet	0.60	0.51	−1.7 ^c	−
Depression	1.85	0.62	+2.1	+
High cognitive activity	0.38	−0.97	−3.2	+
Low unsaturated fat intake ^b	—	—	—	−

Higher total score means greater risk for worse brain health

Microbiome Influence on Brain Health in Acute and Post-acute mTBI Populations

Primary Aim: Measure the influence of acute and post-acute mTBI on the gut microbiome through retrospective and longitudinal observational studies utilizing the Lifestyle for BRAin (LIBRA) model as a measure for overall brain health.

Mindsource Cohort

US-VMP Cohort

Acute mTBI

Post-Acute mTBI

Emergency department
civilian patients diagnosed
with mTBI

Follow up for up to
12 months

Retrospective
analysis from
Veteran patients
that have a
history of mTBI



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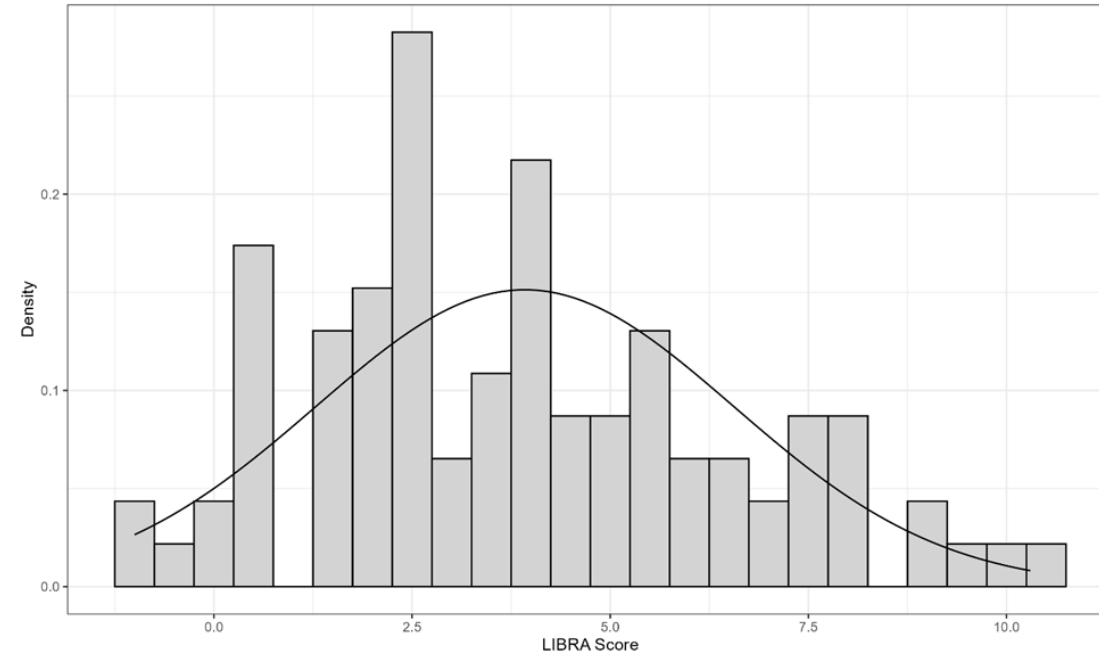
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LIBRA: Post-Acute (US-VMP)

Demographics	Values
Age, mean (SD, min - max)	49.3 (13.5, 24-74)
Race, n (%)	
White	66 (71.7%)
Black	13 (14.1%)
Other	13 (14.1%)
Ethnicity, n (%)	
Non-Hispanic	76 (82.6%)
Hispanic	16 (17.4%)
BMI, mean (SD, min - max)	28.6 (6.1, 20.1-50.0)
Homeless, n (%)	
Yes	30 (32.6%)
No	62 (67.4%)
Times Homeless, mean (SD, min - max)	0.6 (1.1, 0-6)
Multiple Mild TBIs, n (%)	
Yes	56 (60.9%)
No	36 (39.1%)

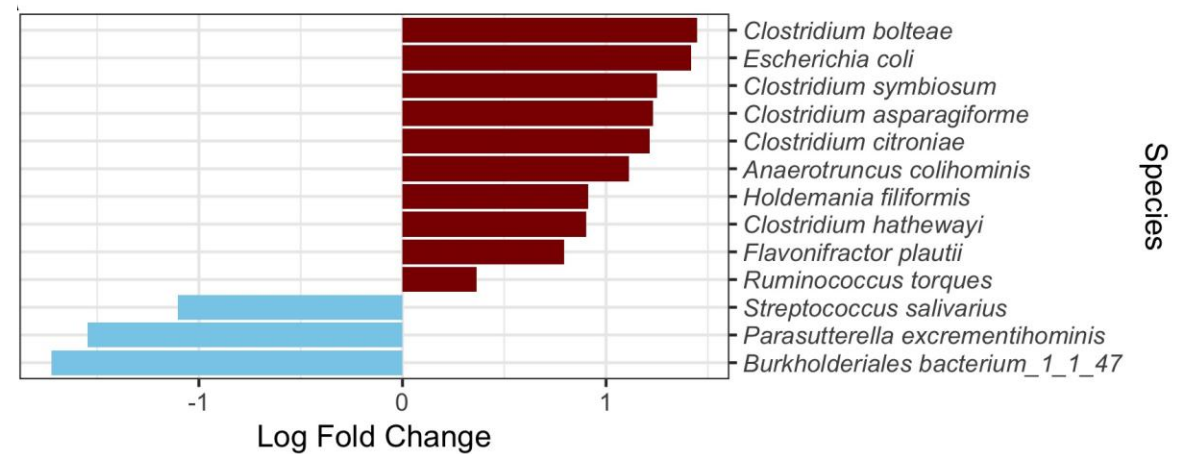
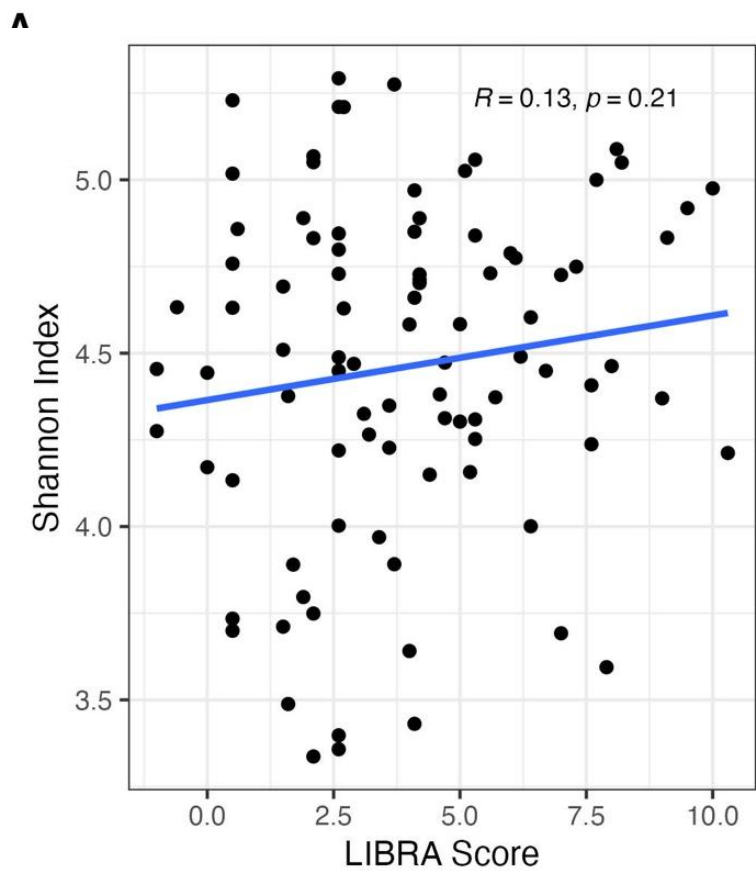
Lifetime mTBI: mean 2 (range 1-7)



Total LIBRA Score

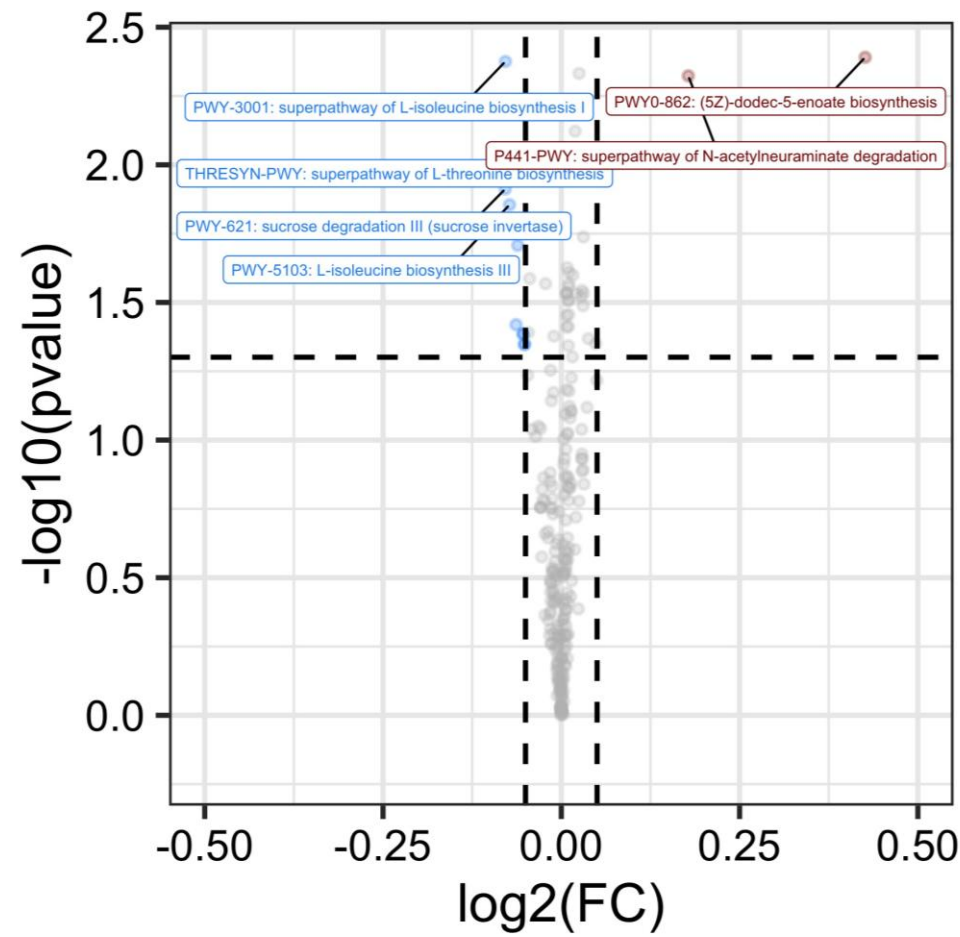
- US-VMP: Mean 3.9, SD = 2.6, Range -1 to 10.3

LIBRA: Post-Acute (US-VMP)



Species	Coefficient	Standard Deviation	P-value	FDR
Increased abundance associated with higher LIBRA score (i.e. worse brain health)				
<i>Clostridium bolteae</i>	1.45	0.52	0.007	0.228
<i>Escherichia coli</i>	1.42	0.53	0.008	0.232
<i>Clostridium symbiosum</i>	1.25	0.55	0.025	0.320
<i>Clostridium asparagiforme</i>	1.23	0.44	0.007	0.228
<i>Clostridium citroniae</i>	1.21	0.41	0.004	0.215
<i>Anaerotruncus colihominis</i>	1.11	0.46	0.019	0.320
<i>Holdemania filiformis</i>	0.91	0.35	0.010	0.235
<i>Clostridium hathewayi</i>	0.90	0.44	0.041	0.396
<i>Flavonifractor plautii</i>	0.79	0.38	0.042	0.396
<i>Ruminococcus torques</i>	0.37	0.16	0.024	0.320
Increased abundance associated with lower LIBRA score (i.e. better brain health)				
<i>Streptococcus salivarius</i>	-1.10	0.45	0.017	0.320
<i>Parasutterella excrementihominis</i>	-1.55	0.50	0.002	0.215
<i>Burkholderiales bacterium_1_1_47</i>	-1.72	0.62	0.007	0.228

LIBRA: Post-Acute (US-VMP)

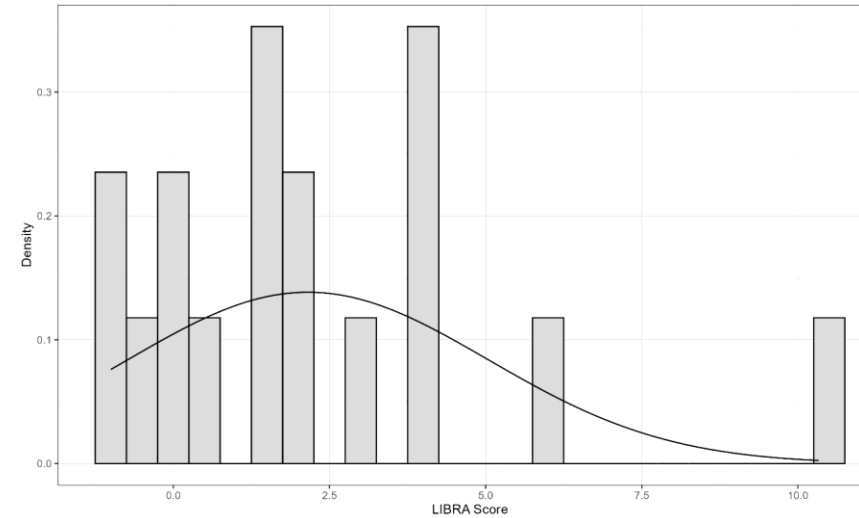


Metabolic Category	Pathway	Log2-Fold Change $\pm$ SD	p-value
Energy Utilization	Glycolysis I (from glucose 6-phosphate)	0.03 ± 0.05	0.029
	Starch degradation V	-0.04 ± 0.04	0.026
	Galactose degradation I (Leloir pathway)	-0.05 ± 0.06	0.041
	D-galactose degradation V (Leloir pathway)	-0.05 ± 0.06	0.041
	Sucrose degradation III (sucrose invertase)	-0.08 ± 0.13	0.012

LIBRA: Acute (Mindsource)

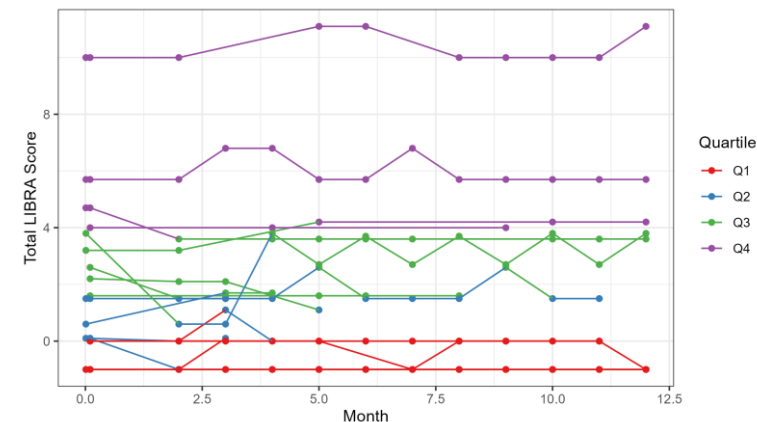
Demographics	Values
Age, mean (SD, min-max)	33 (12, 20-57)
Sex, n (%)	
Male	11 (64.7%)
Female	6 (35.3%)
Race, n (%)	
White	8 (47%)
Black	2 (11.7%)
Other	7 (41.3%)
Ethnicity	
Non-Hispanic	12 (70.6%)
Hispanic	5 (29.4%)
Homeless, n (%)	
Yes	3 (17.6%)
No	14 (82.4%)

Lifetime mTBI: mean 1.7
(range 1-5)

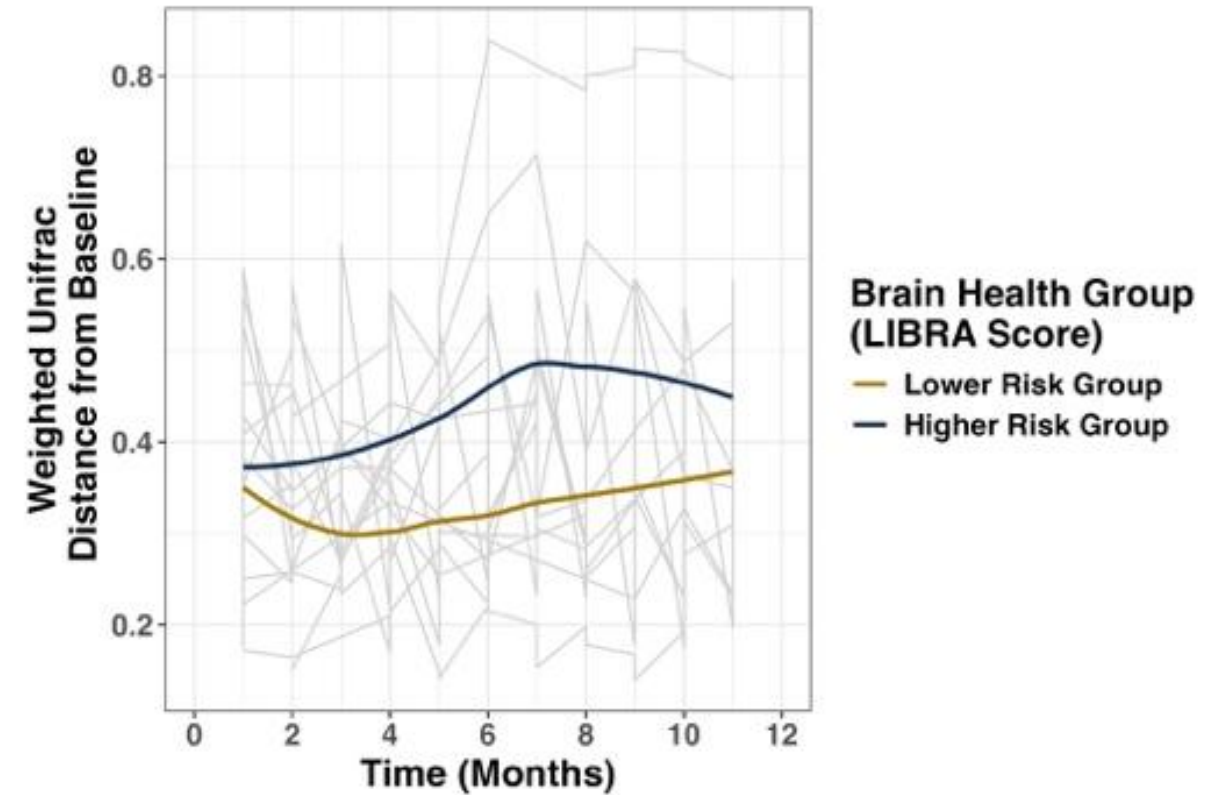
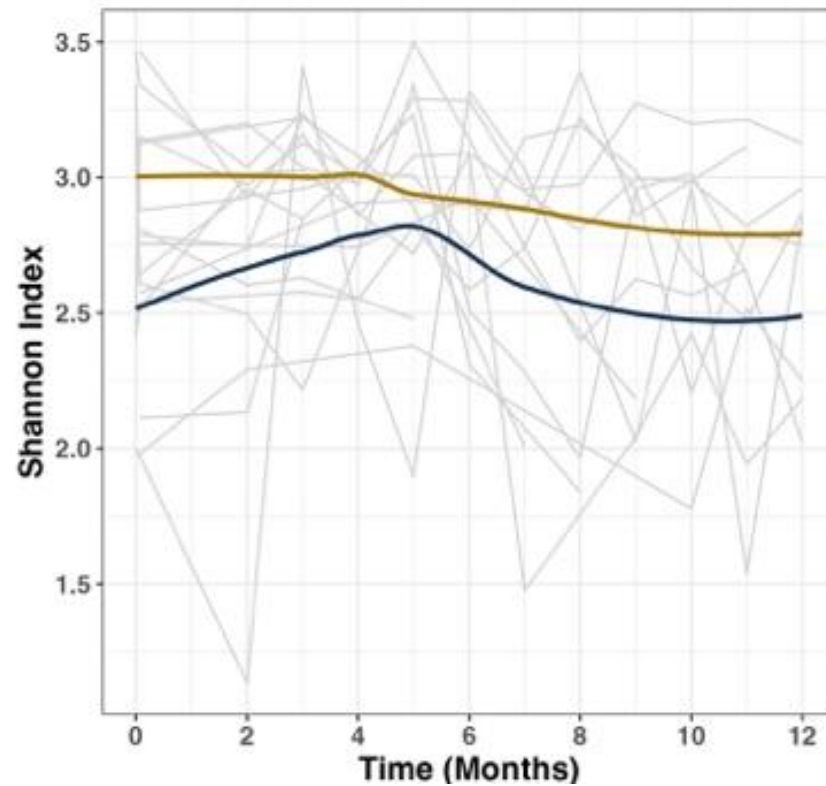


Total LIBRA Score

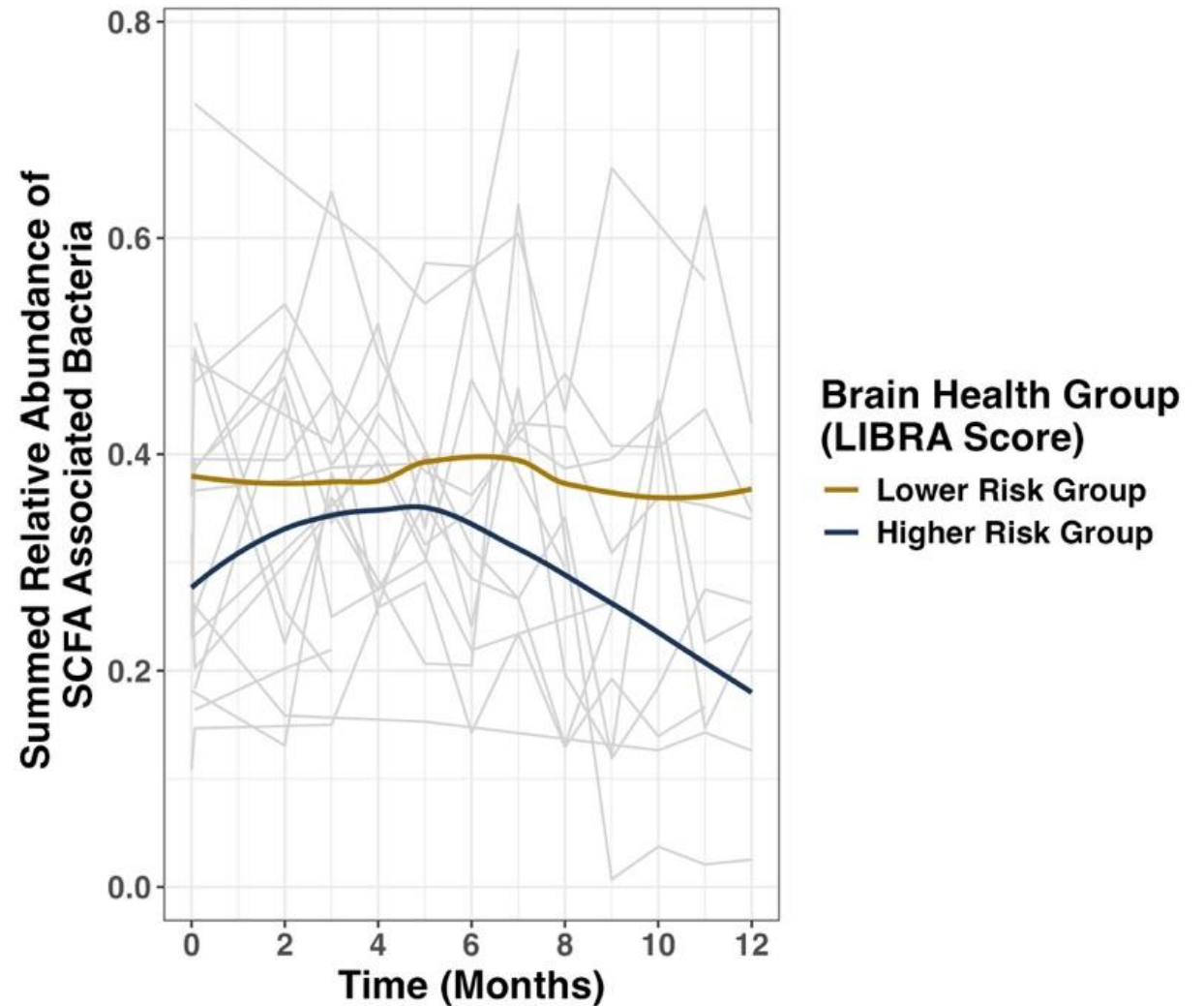
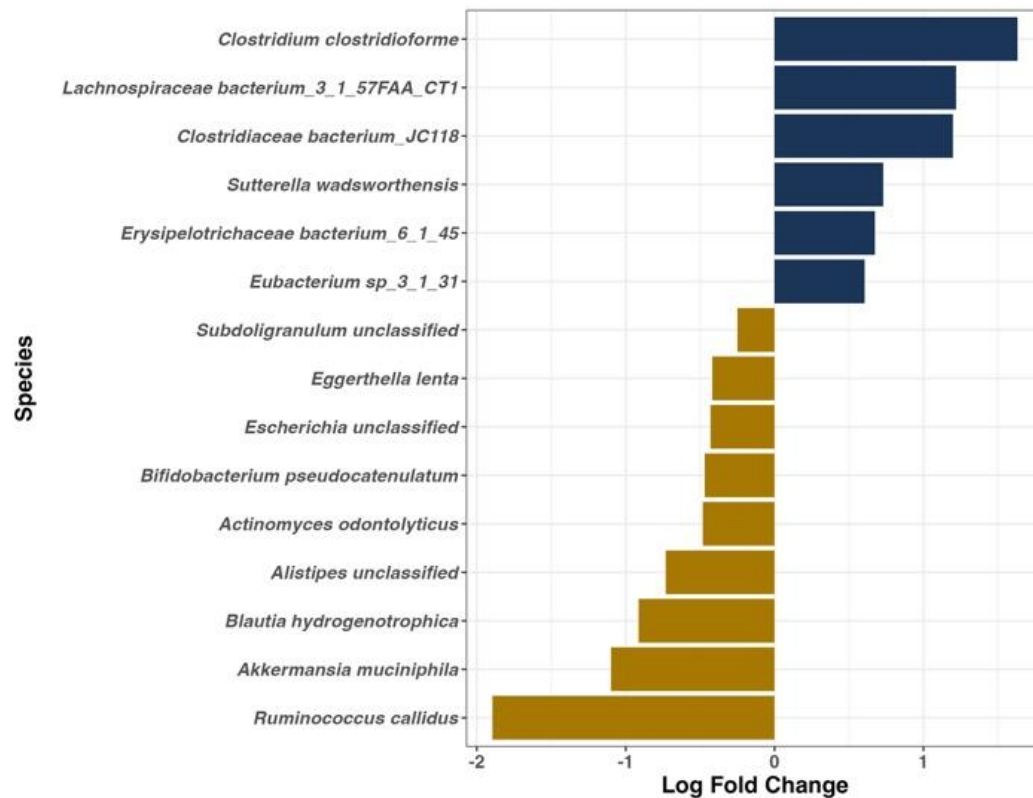
- mTBI ED: Mean 2.1, SD = 0.4, Range -1 to 11.1
- US-VMP: Mean 3.9, SD = 2.6, Range -1 to 10.3



LIBRA: Acute (Mindsource)



LIBRA: Acute (Mindsource)





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Thank you

