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U.S. Department
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The Brain, Gut, & Microbiome- Implications Regarding Short- and Long- Term Recovery Post-Brain Injury

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Disclaimer and Disclosure

This presentation is based on work supported, in part, by the Department of Veterans Affairs, but does not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

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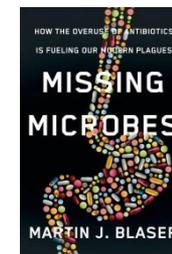
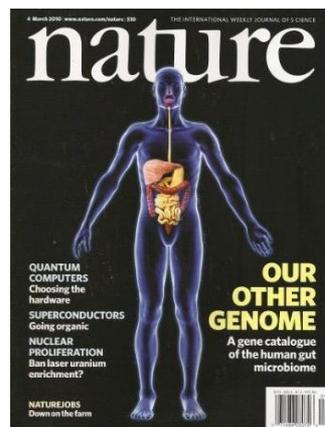
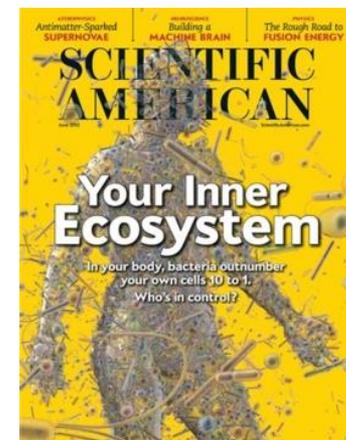
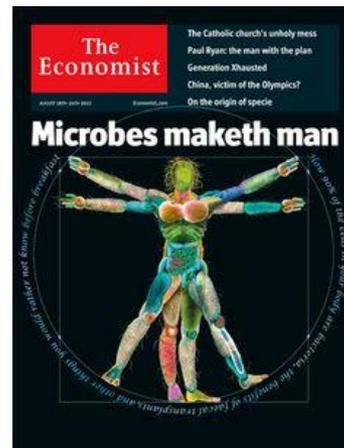
House, Senate negotiators reach budget deal



PHOTOS | Notable deaths of 2013

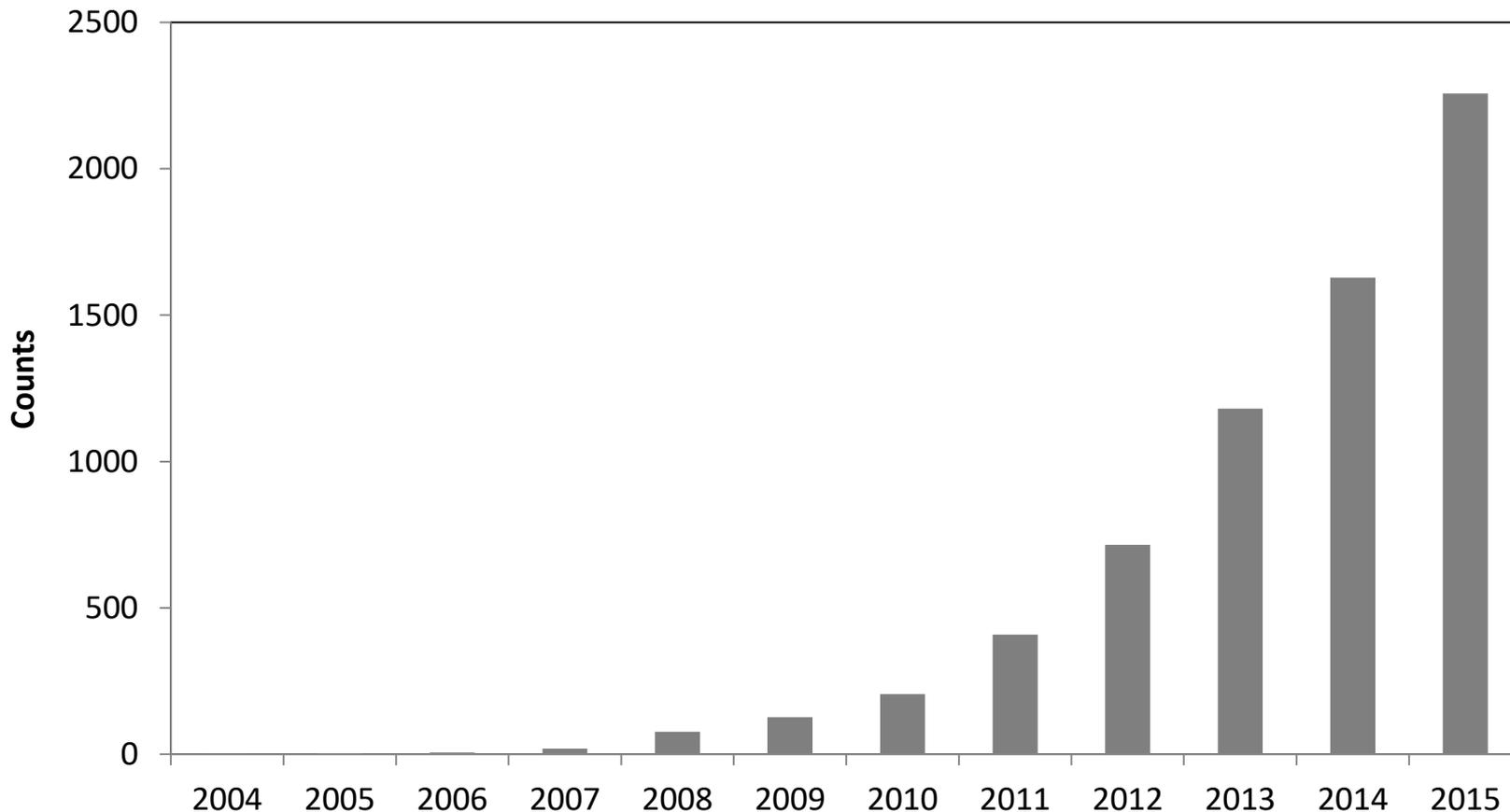


The microbes in your gut may be making you fat or keeping you thin





"Microbiome" Topic Search in Web of Science





What are microbes?

Bacteria

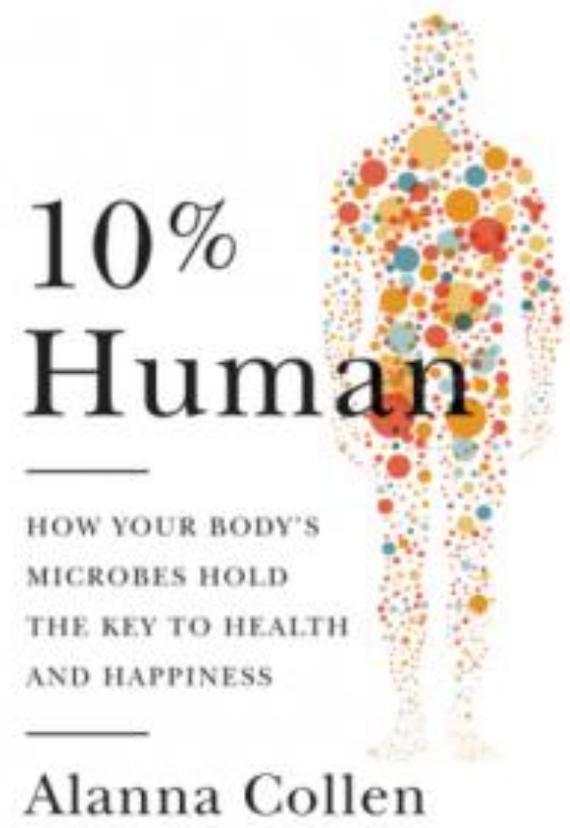
Archaea

Fungi

Protists

Viruses

Microscopic Animals



10%
Human

HOW YOUR BODY'S
MICROBES HOLD
THE KEY TO HEALTH
AND HAPPINESS

Alanna Collen

A map of diversity in the human microbiome



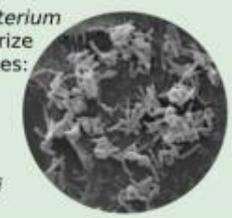
Streptococcus dominates the oral cavity with *S. mitis* > 75% in the **cheek**

Propionibacterium lives on the skin and **nose** of most people



Many *Corynebacterium* species characterize different body sites:

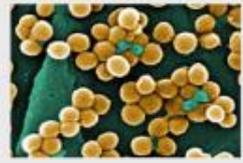
- C. matruchoti* the **plaque**
- C. accolens* the **nose**
- C. croppenstedtii* the **skin**



Lactobacillus species (*L. gasseri*, *L. jensenii*, *L. crispatus*, *L. iners*) are predominant but mutually exclusive in the **vagina**



Staphylococcus epidermidis colonizes external body sites



- Commensal microbes
- ☆ Potential pathogens

The four most abundant phyla

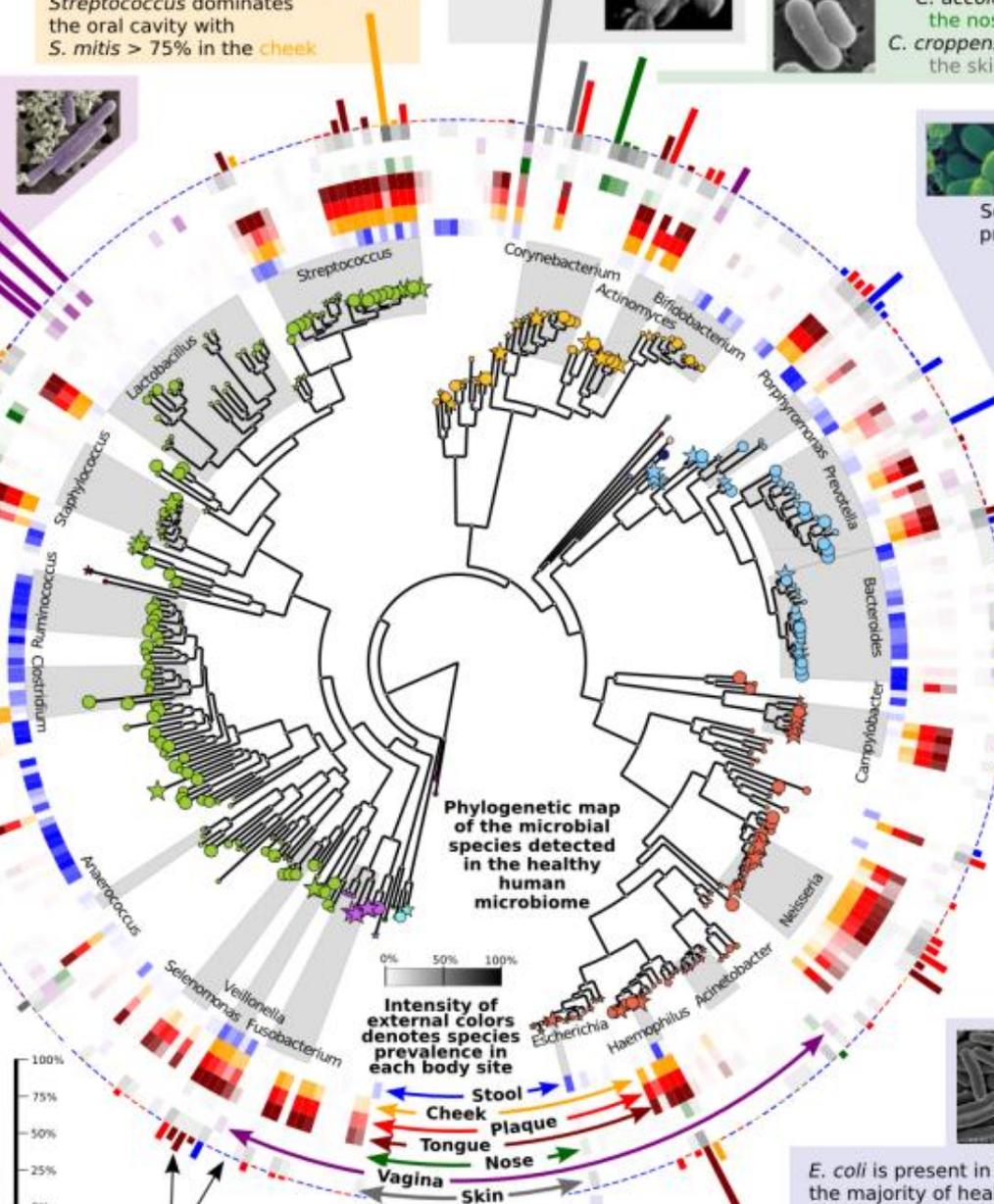
- Actinobacteria
- Bacteroidetes
- Firmicutes
- Proteobacteria

Low abundance phyla

- Chloroflexi
- Cyanobacteria
- Euryarchaeota
- Fusobacteria
- Lentisphaerae
- Spirochaetes
- Synergistetes
- Tenericutes
- Thermi
- Verrucomicrobia

National Institutes of Health
Human Microbiome Project

N. Segata & C. Huttenhower
<http://huttenhower.sph.harvard.edu>
generated using Cytoscape and R (3/10/10 from Huttenhower analysis)



Bar lengths indicate microbial abundance (colored by body site of greatest prevalence)



Several *Prevotella* species are present in the gastrointestinal tract. *P. copri* is present in 19% of the subjects and dominates the **intestinal** flora when present



Microscopy from <http://kacmap.wishartlab.com>

Bacteroides is the most abundant genus in the **gut** of almost all healthy subjects



Campylobacter includes opportunistic pathogens, but members live in the oral cavities of most healthy people in the cohort

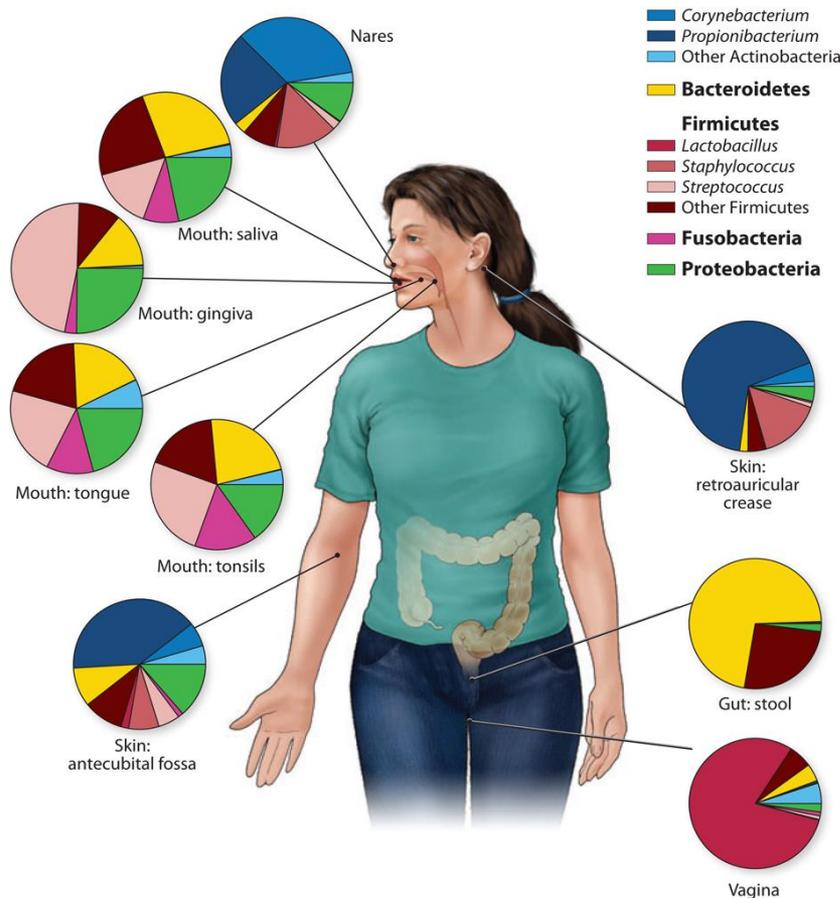


E. coli is present in the **gut** of the majority of healthy subjects but at very low abundance





Genus- and phylum-level classification of bacteria colonizing a composite subject



Grice EA, Segre JA. The Human Microbiome: Our Second Genome. *Annual review of genomics and human genetics*. 2012;13:151-170. doi:10.1146/annurev-genom-090711-163814.



Conceptual Terms	Operational Definitions
Alpha Diversity (α -Diversity)	A measure in microbial ecology of “species” diversity, specifically, the diversity within a sample. For example, one measure of α -diversity, observed species (or observed OTUs [operational taxonomic units]), simply reflects the number of different OTUs present in the sample, a measure of species richness in the sample.
Beta Diversity (β -Diversity)	A measure in microbial ecology of species diversity, specifically, the diversity between samples.
Dysbiosis	Disruption of the gut microbial diversity and community structure, typically due to reductions in beneficial bacteria and overgrowth of harmful bacteria, yeast, and or parasites.

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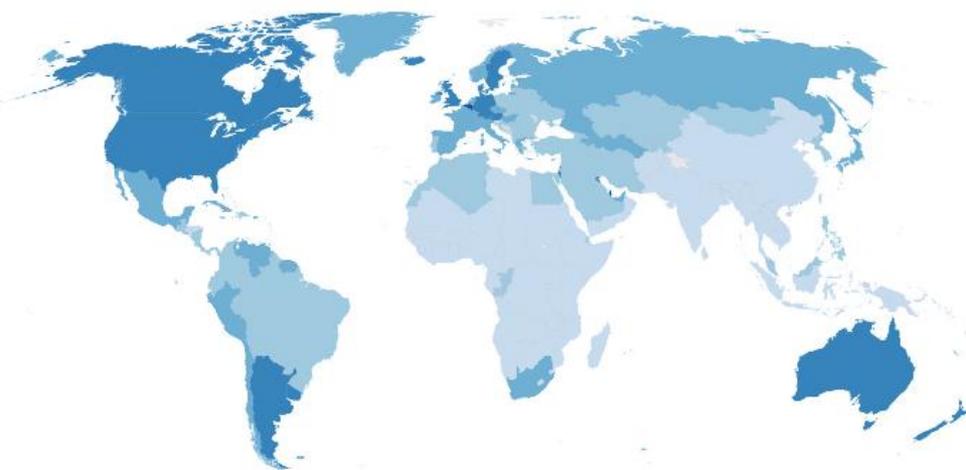


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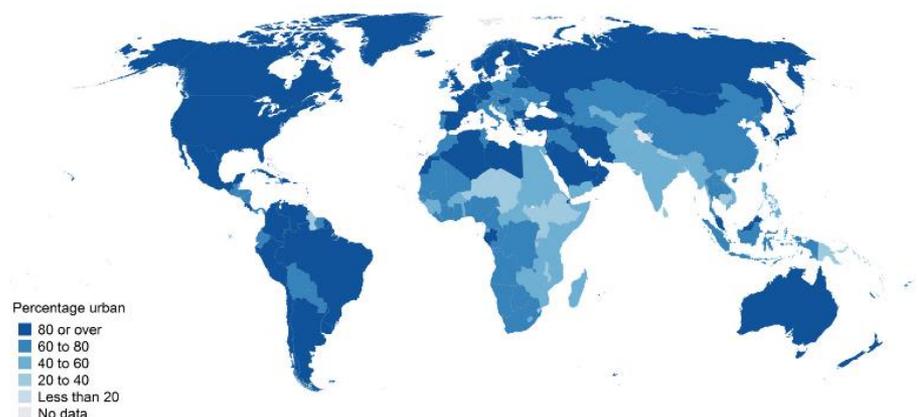


World Urbanization

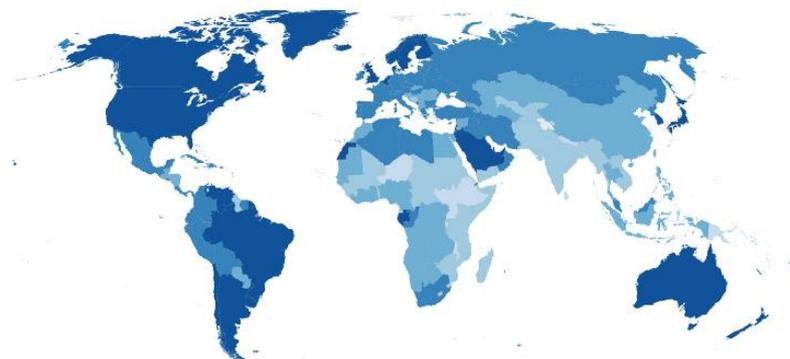
1950



2050



2014





RESEARCH ARTICLE

MICROBIOLOGY

Walls talk: Microbial biogeography of homes spanning urbanization

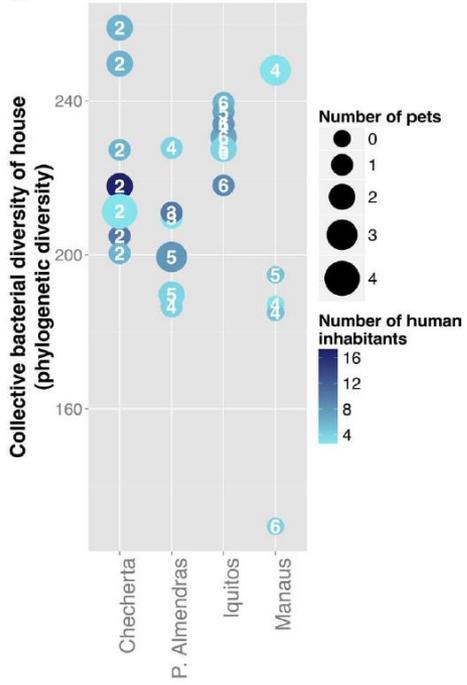
2016 © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC). 10.1126/sciadv.1501061

Jean F. Ruiz-Calderon,^{1*} Humberto Cavallin,^{2*} Se Jin Song,^{3*} Atila Novoselac,⁴ Luis R. Pericchi,⁵ Jean N. Hernandez,¹ Rafael Rios,⁶ Oralee H. Branch,⁷ Henrique Pereira,⁸ Luciana C. Paulino,⁹ Martin J. Blaser,¹⁰ Rob Knight,¹¹ Maria G. Dominguez-Bello^{1,10†}



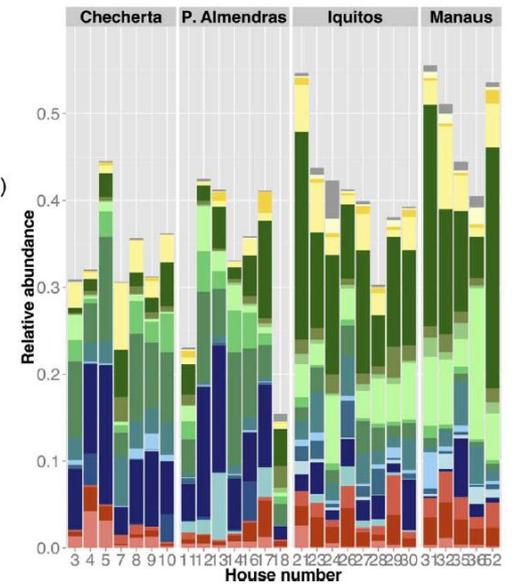


D



C

- Firmicutes (Lactobacillaceae)
- Firmicutes (Streptococcaceae)
- Proteobacteria (Pseudomonadaceae)
- Archaea (Halobacteriaceae)
- Actinobacteria (Actinosynnemataceae)
- Actinobacteria (Intrasporangiaceae)
- Cyanobacteria (Xenococcaceae)
- Firmicutes (Aerococcaceae)
- Proteobacteria (IChromatiaceae)
- Proteobacteria (Rhodobacteraceae)
- Actinobacteria (*Brachybacterium*)
- Actinobacteria (*Brevibacterium*)
- Actinobacteria (*Corynebacterium*)
- Proteobacteria (Aeromonadaceae)
- Proteobacteria (Comamonadaceae)
- Proteobacteria (*Enhydrobacter*)
- Bacteroidetes (Weeksellaceae)
- Firmicutes ([Exiguobacteraceae])
- Firmicutes ([Tissierellaceae])
- Proteobacteria (Acetobacteraceae)



The biodiversity hypothesis and allergic disease: world allergy organization position statement

Tari Haahtela^{1*}, Stephen Holgate², Ruby Pawankar³, Cezmi A Akdis⁴, Suwat Benjaponpitak⁵, Luis Caraballo⁶, Jeffrey Demain⁷, Jay Portnoy⁸, Leena von Hertzen¹, and WAO Special Committee on Climate Change and Biodiversity

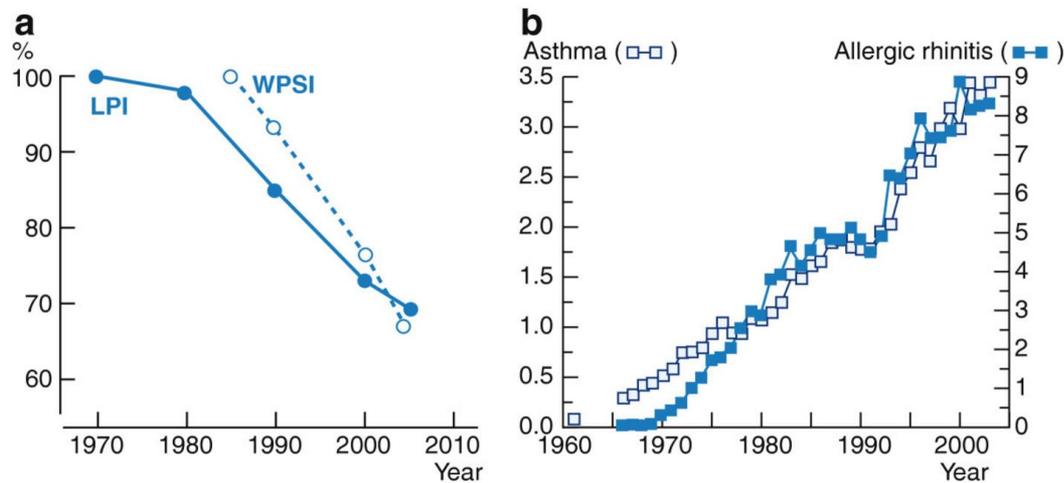
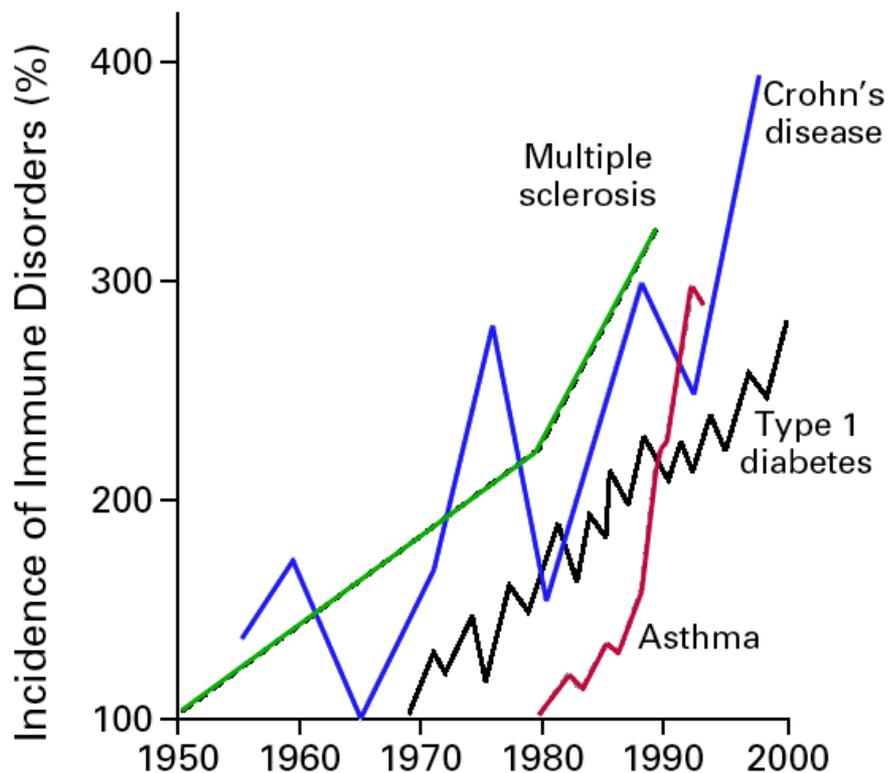


Figure 1

Two global megatrends in biodiversity and public health. (a) Declining biodiversity (percentage change) since 1970 as measured by two indices. WPSI=Waterbird Population Status Index; LPI=Living Planet Index [14]. (b) Increasing trends in the prevalence of inflammatory civilization diseases, asthma and allergic rhinitis among military conscripts in 1966-2003 [165] as an example (modified from ref. [14]).



The Increasing Incidence of Immunoregulatory Disorders





“Old Friends” and a Failure of Immunoregulation

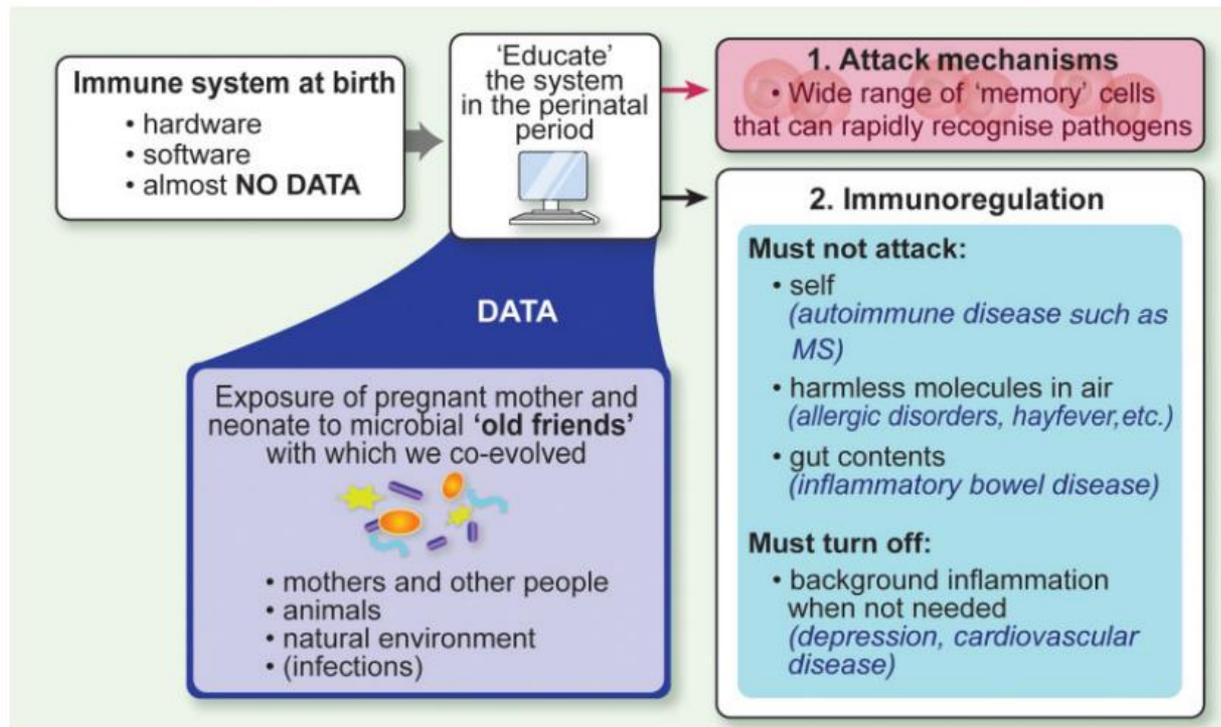
One factor contributing to increases in chronic inflammatory disorders in high-income countries is thought to be failing immunoregulation, attributable to reduced exposure to the microbial environment within which the mammalian immune system co-evolved.^{1,2}

1. Rook GA, Raison CL, Lowry CA. Microbial 'old friends', immunoregulation and socioeconomic status. *Clin Exp Immunol*. 2014;177(1):1-12.

2. Haahtela T, Holgate S, Pawankar R, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *World Allergy Organ J*. 2013;6(1):3.



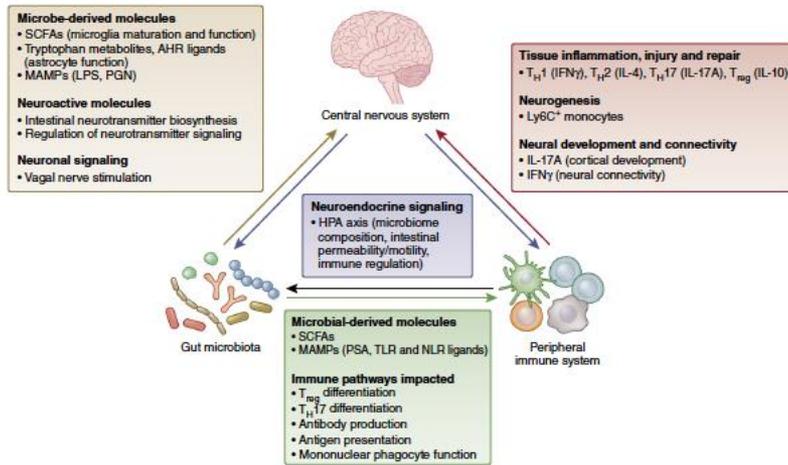
“Old Friends” and a Failure of Immunoregulation





Interactions between the microbiota, immune and nervous systems in health and disease

Thomas C Fung, Christine A Olson & Elaine Y Hsiao

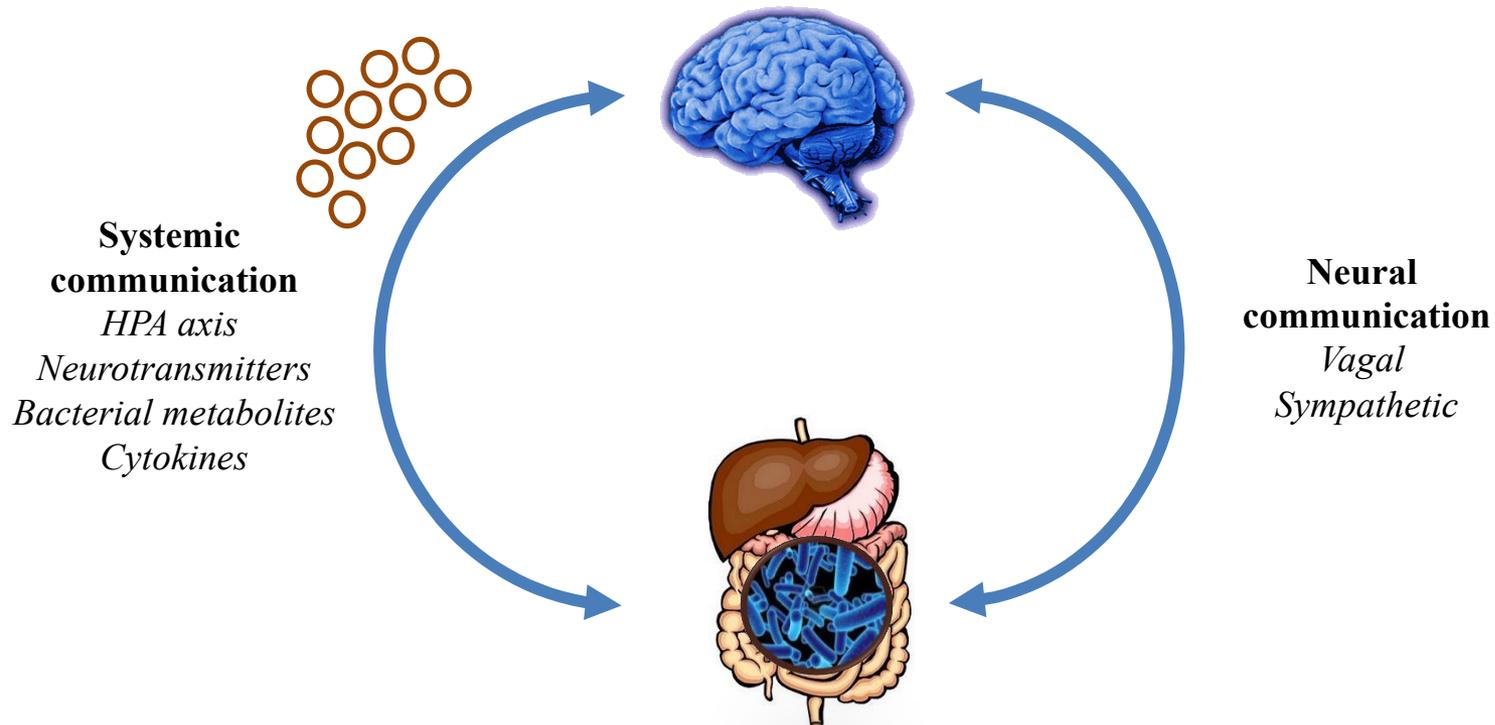


Debbie Maize/Springer Nature

Gut microbial changes	Immunological changes	Effects on CNS function
Segmented filamentous bacteria	T_H17	CNS inflammation (MS, EAE)
<i>Bacteroides fragilis</i>	PSA, SCFA → T_H17	
SCFA-producing bacteria	T_H17 → IL-10	
ABX-treatment	CD4 ⁺ IELs	CNS inflammation (MS, EAE)
	LAG-3	
	T_H17 → IL-17A	
Microbial dysbiosis	IL-6 → T_H17	Social communication (ASD)
	$\gamma\delta$ T cells → IL-17A	CNS injury (stroke, spinal cord injury)
SCFA-producing bacteria	T_H17 → T_H2 → IL-4	
Probiotics (VSL3, <i>Bifidobacterium</i> , <i>Lactobacillus</i>)	Ly6C ⁺ monocytes	Neurogenesis
	Pro-inflammatory mediators	Mood disorders (anxiety, depression)
<i>Streptococcus</i>	B cells → Auto-antibodies	CNS autoimmunity (PANDAS) Eating disorders
<i>E. coli</i>		
Microbial infection	Amyloid- β peptides	Neurodegeneration (Alzheimer's, Parkinson's)
Enterobacteriaceae	Pro-inflammatory mediators	

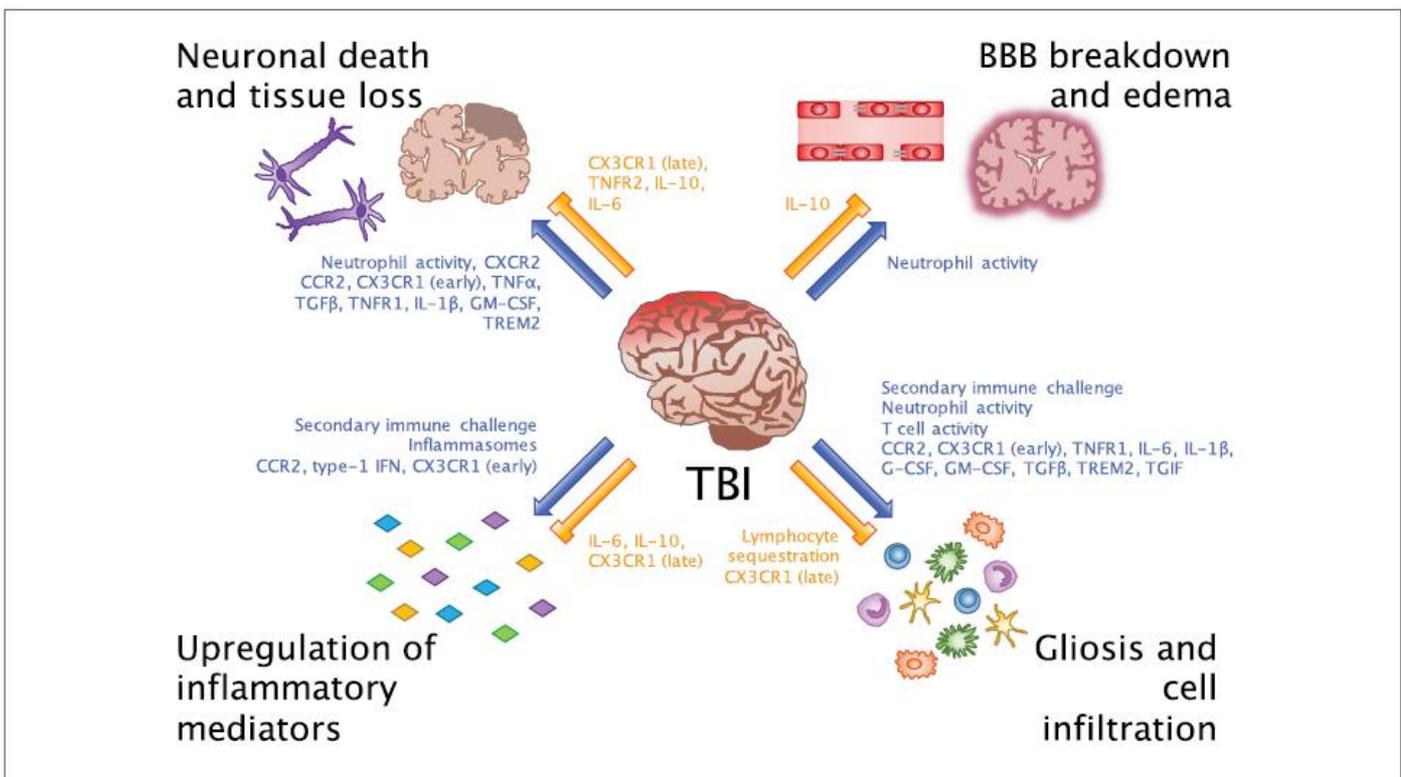
Debbie Maize/Springer Nature

Bidirectional Communication Channels between the Gut Microbiome, the Gut, and the Brain

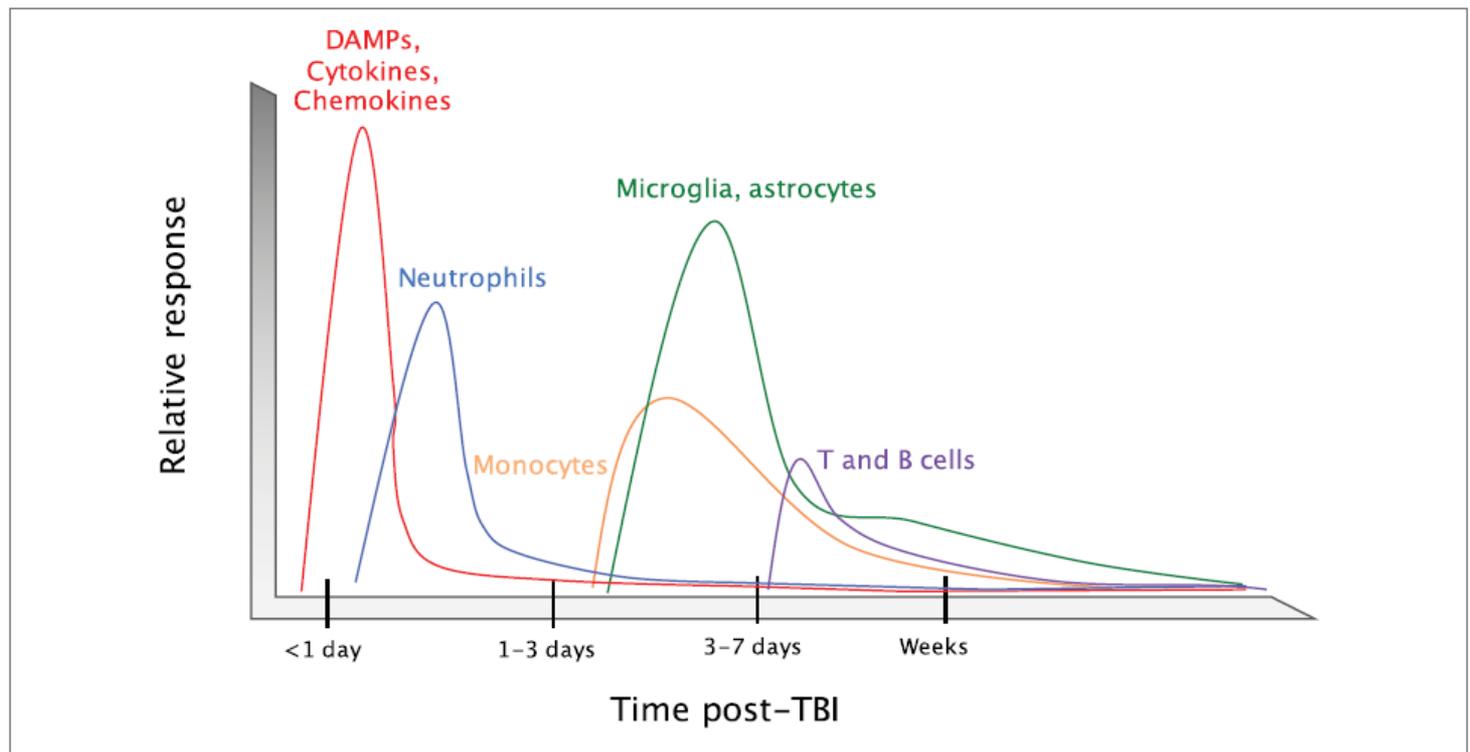


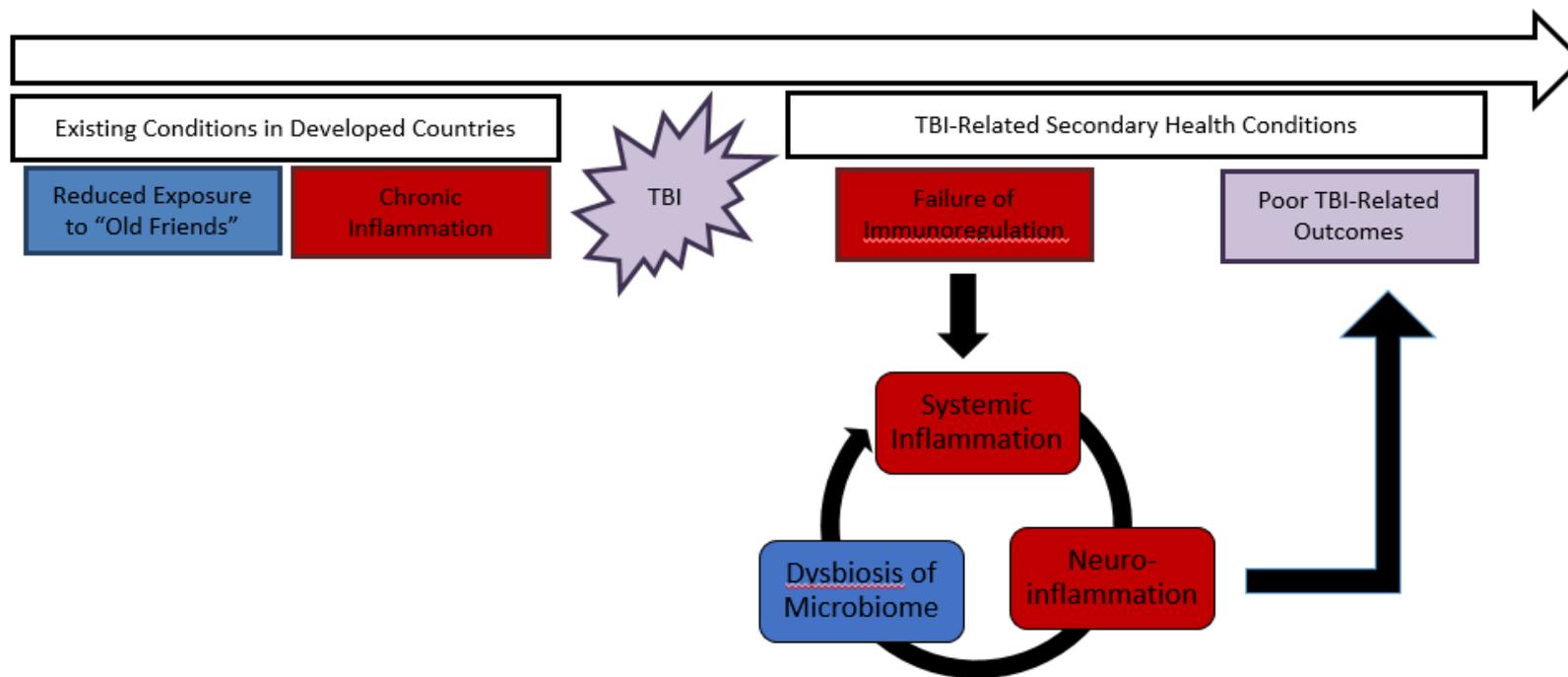
Sudo et al. (2004) discovered that germ-free mice have an exaggerated hypothalamic-pituitary-adrenal (HPA) axis response to restraint stress – an effect that was reversed by monocolonization with a particular *Bifidobacterium* species.

Beneficial and detrimental roles for the immune system in TBI



Beneficial and detrimental roles for the immune system in TBI





Veteran Microbiome Study

Inclusion criteria

- Veterans between ages 18-89 years of age at the time of enrollment
- Must be able to provide signed and dated informed consent
- Willing and able to provide oral cavity, skin and/or gastrointestinal tract specimens

Research Opportunity for Veterans

We are seeking Veterans to participate in a research study about microorganisms on the body and in the environment.



Participants will attend one session to complete questionnaires and provide samples. Compensation will be provided.

For more information contact:
Kelly Stearns-Yoder
303-399-8020 x6103



PI: Lisa Brenner, PhD | COMIRB #: 15-1885 | Version Date: 12-15-2015

Lisa A. Brenner, Ph.D., Kelly Stearns, M.A., Christopher A. Lowry, LtCol Andrew J. Hoisington, Ph.D., PE, Teodor T. Postolache, M.D.



Measure	Time (min)	Purpose
<i>Visit at ECHCS</i>		
UWRAP	5	Safety
Rocky Mountain MIRECC Demographics Form	5	Sample Characteristics
Structured Clinical Interview for DSM-V Axis I Disorders (SCID)	30	Sample Characteristics
Ohio State University TBI-ID (OSU-TBI-ID)	25	Sample Characteristics
PTSD Symptom Checklist 5 (PCL-5)	5	Sample Characteristics
Outcome Questionnaire (OQ-45)	10	Sample Characteristics
Short Form 36 Health Survey (SF-36)	10	Sample Characteristics
Harvard Food Frequency Questionnaire Booklet	20	Sample Characteristics
Insomnia Severity Index (ISI)	5	Sample Characteristics
Oral Microbiome	5	Primary Aim
Skin Microbiome	5	Primary Aim
<i>After Visit</i>		
Gut Microbiome	5	Primary Aim



Active Problems: (4 of 4)

SNOMED	Description	Onset Date	Last Updated	Location
A*	Calcaneal spur (SCT 9526000)	Jul 31 2011	Aug 18 2011	General Medicine
A*	Other employment (ICD-9-CM 492.8) ICD-9-CM Text: Other Employment		Dec 15 2010	45 Clinic Patient
A*	Complete rupture of rotator cuff, non-traumatic (ICD-9-CM 727.61) ICD-9-CM Text: Complete Rupture Of Rotator Cuff		Dec 15 2010	45 Clinic Patient
A*	Skin Carcinoma (ICD-9-CM 173.9) ICD-9-CM Text: Other Malignant Neoplasm Of Skin, Site Unclassified	Nov 23 2010	Dec 15 2010	45 Clinic Patient

Explanatory Text:

- This problem has a SNOMED Concept Term [SNOMED: C.T] code. SNOMED is a system written by physicians for physicians.
- The I.C. (Environmental Contaminants) after the problem indicates that this problem is service-connected.
- The ICD code is also shown after the problem text.

The problems list on the Problems tab can be configured to show active, inactive, both active and inactive combined, or removed problems. Treatment factors, SNOMED CT codes, and ICD codes display right after the problem text.



Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?
 Very Satisfied Satisfied Moderately Satisfied Dissatisfied Very Dissatisfied
 0 1 2 3 4
5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?
 Not at all
 Noticeable A Little Somewhat Much Very Much Noticeable
 0 1 2 3 4
6. How WORRIED/DISTRESSED are you about your current sleep problem?
 Not at all
 Worried A Little Somewhat Much Very Much Worried
 0 1 2 3 4
7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?
 Not at all
 Interfering A Little Somewhat Much Very Much Interfering
 0 1 2 3 4

Outcome Questionnaire (OQ®-45.2)

Instructions: Looking back over the last week, including today, help us understand how you have been feeling. Read each item carefully and mark the box under the category which best describes your current situation. For this questionnaire, work is defined as employment, school, housework, volunteer work, and so forth. Please do not make any marks in the shaded areas.

ID:

Date:

	Always					SD IR SR				
	Never	Rarely	Sometimes	Frequently	Always	DO NOT	IR	SR	DO NOT	SR
1. I get along well with others.	4	3	2	1	0					
2. I tire quickly.	0	1	2	3	4					
3. I feel no interest in things.	0	1	2	3	4					
4. I feel stressed at work/school.	0	1	2	3	4					
5. I blame myself for things.	0	1	2	3	4					
6. I feel irritated.	0	1	2	3	4					
7. I feel unhappy in my marriage/significant relationship.	0	1	2	3	4					
8. I have thoughts of ending my life.	0	1	2	3	4					
9. I feel weak.	0	1	2	3	4					
10. I feel fearful.	0	1	2	3	4					
11. After heavy drinking, I need a drink the next morning to get going. (If you do not drink, mark "never")	4	3	2	1	0					
12. I find my work/school satisfying.	4	3	2	1	0					
13. I am a happy person.	4	3	2	1	0					
14. I work/study too much.	0	1	2	3	4					
15. I feel worthless.	0	1	2	3	4					
16. I am concerned about family troubles.	0	1	2	3	4					
17. I have an unfulfilling sex life.	0	1	2	3	4					
18. I feel lonely.	0	1	2	3	4					
19. I have frequent arguments.	0	1	2	3	4					
20. I feel loved and wanted.	4	3	2	1	0					
21. I enjoy my spare time.	4	3	2	1	0					
22. I have difficulty concentrating.	0	1	2	3	4					
23. I feel hopeless about the future.	0	1	2	3	4					
24. I like myself.	4	3	2	1	0					
25. Disturbing thoughts come into my mind that I cannot get rid of.	0	1	2	3	4					
26. I feel annoyed by people who criticize my drinking (or drug use). (If not applicable, mark "never")	0	1	2	3	4					
27. I have an upset stomach.	0	1	2	3	4					
28. I am not working/studying as well as I used to.	0	1	2	3	4					
29. My heart pounds too much.	0	1	2	3	4					
30. I have trouble getting along with friends and close.	0	1	2	3	4					
31. I am satisfied with my life.	4	3	2	1	0					
32. I have trouble at work/school because of drinking or drug use. (If not applicable, mark "never")	0	1	2	3	4					
33. I feel that something bad is going to happen.	0	1	2	3	4					
34. I have sore muscles.	0	1	2	3	4					
35. I feel afraid of open spaces, of driving, or being on buses, subways, and so forth.	0	1	2	3	4					
36. I feel nervous.	0	1	2	3	4					
37. I feel my love relationships are full and complete.	4	3	2	1	0					
38. I feel that I am not doing well at work/school.	0	1	2	3	4					
39. I have too many disagreements at work/school.	0	1	2	3	4					
40. I feel something is wrong with my mind.	0	1	2	3	4					
41. I have trouble falling asleep or staying asleep.	0	1	2	3	4					
42. I feel blue.	0	1	2	3	4					
43. I am satisfied with my relationships with others.	4	3	2	1	0					
44. I feel angry enough at work/school to do something I might regret.	0	1	2	3	4					
45. I have headaches.	0	1	2	3	4					
Total=										

Veteran Microbiome Study - Demographic Characteristics (n=188)

Age	Mean 46.8; Range 24-77; 14.5% - 20's, 26.5% - 30's, 13% - 40's, 26% - 50's, 17.5% - 60's, 2.5% - 70's
Gender	85.5% Male
Racial Background	64% - Caucasian, 21.5% - African-American, 2.5% - Native-American, 1.5% - Asian, 3% - Multiracial, 7.5% - Other
Education	13% - High School, 53% - Some College/Associate Degree, 26% - Bachelor Degree, 8% - Master/Doctoral
Marital Status	32.5% - Married, 28.5% - Single, 4.5% - Cohabiting, 4.5% - Widowed, 30% - Divorced/Separated
Employment	26%-Full-Time, 8.5%-Part-Time, 18% - Unemployed (not seeking), 22% - Unemployed (seeking), 25.5% - Retired
Student	13.5% - Full-Time, 5.5% - Part-Time
Currently Homeless	9%
Lifetime Homelessness	61%-never, 15%- one time, 24%-more than once

Veteran Microbiome Study - Military Characteristics

Service Era	Pre-Korean - 0%; Korean - 1.5%, Post-Korean - 15; Vietnam - 36.5%, Desert Storm - 26.5%, OIF/OEF - 46%
Year of Separation from Military	Mean 1997; Range 1959-2017
Deployments	Mean 2; Range 0-15
Combat Tours	Mean 1; Range 0-8 (1 tour - 21.5%, 2 tours - 15%, 3 tours - 5%)

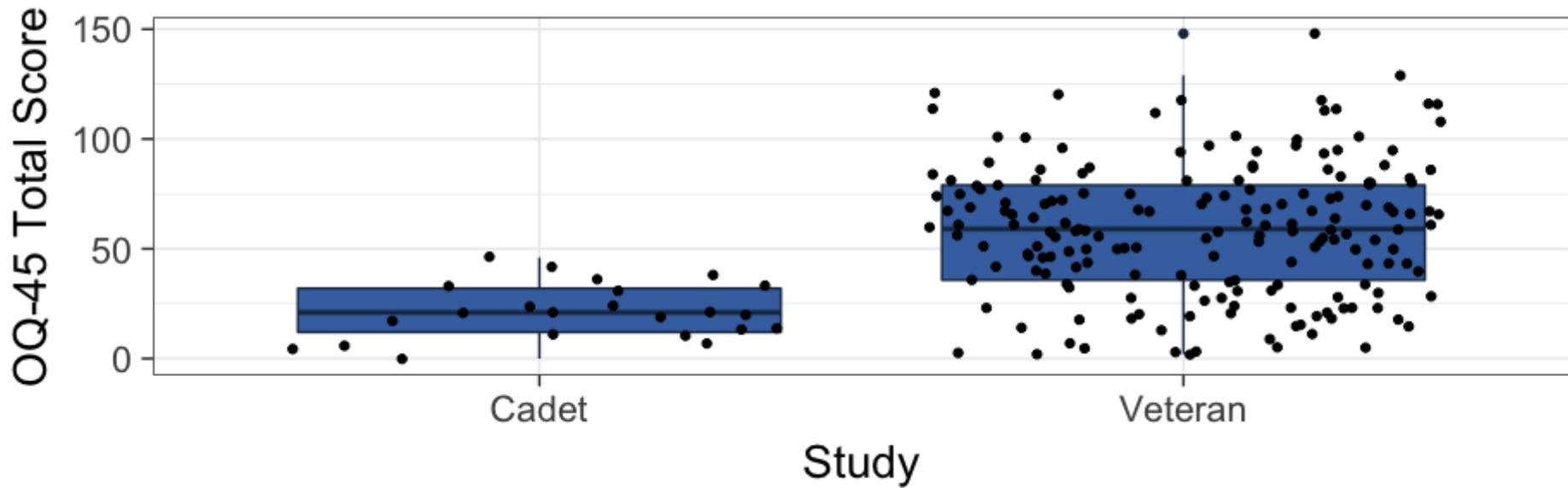
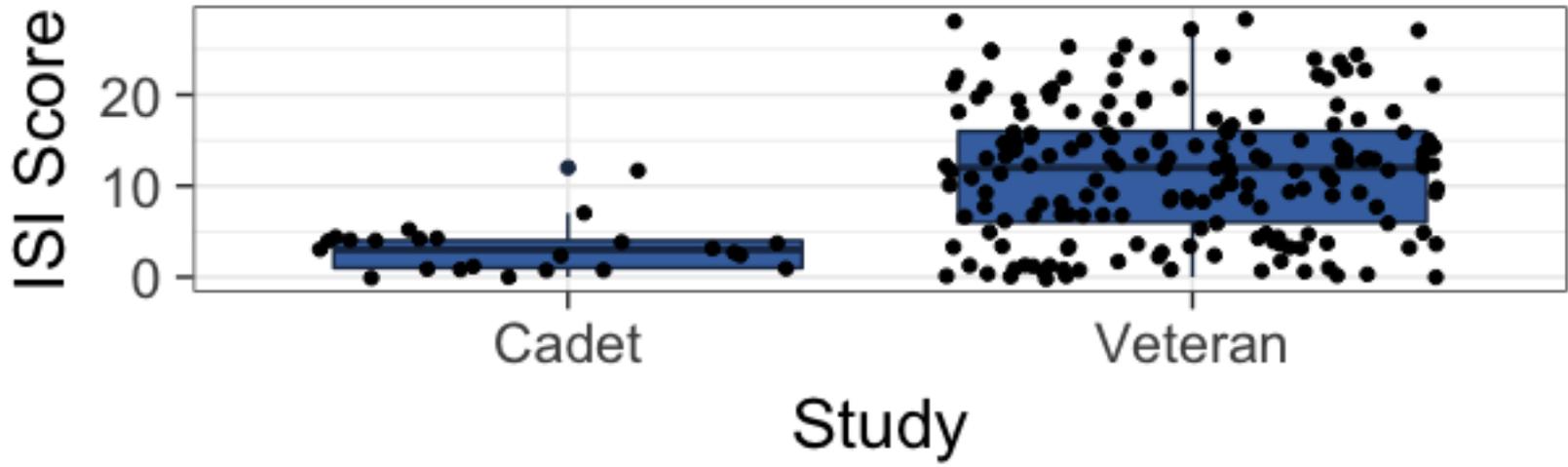
1,246 years or 6.6 years/person

Veteran Microbiome Study – TBI (Preliminary)

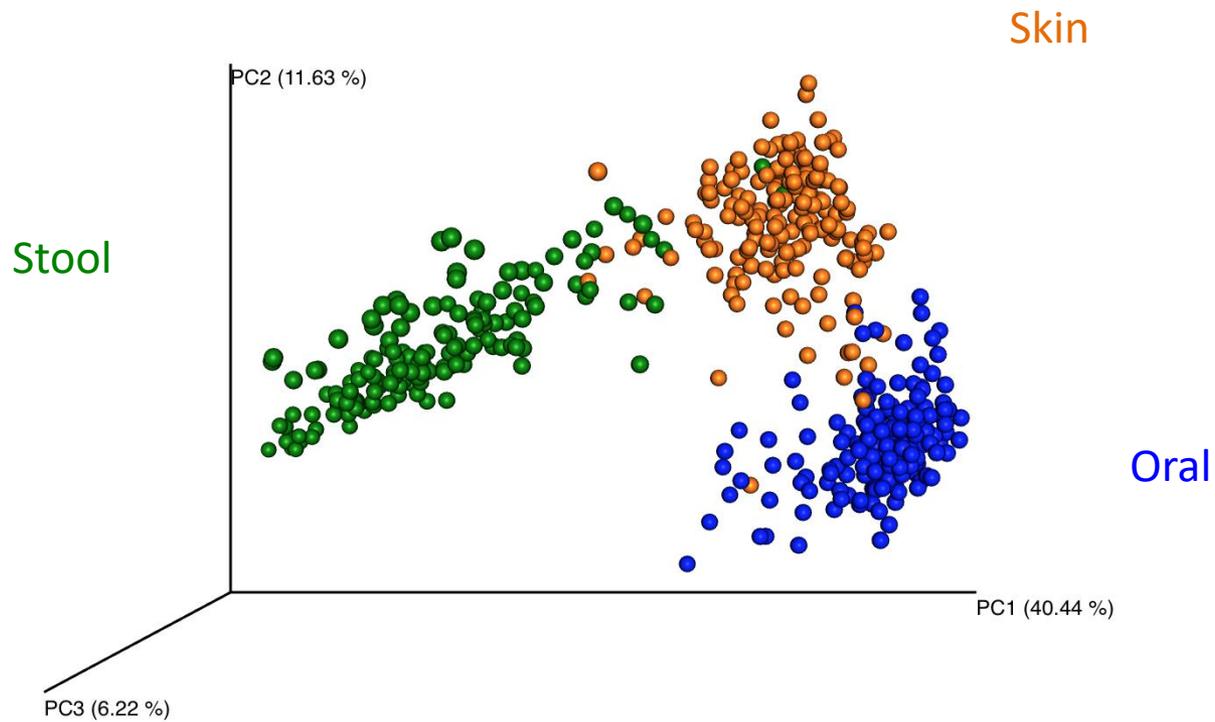
Traumatic Brain Injury (n miss = 1)	
Yes	133 (71.1%)
No	54 (28.9%)
Moderate or Severe Brain Injury	
Yes	23 (12.2%)
No	165 (87.8%)
Number of Traumatic Brain Injuries (n = 133)	2.50 ± 1.74 (1-11)

Veteran Microbiome Study – Mental Health Scores

Variable	N (%) or Mean ± SD (range)
Insomnia Severity Index² (nmiss = 3)	
Severe Clinical Insomnia	21 (11.3%)
Moderate Clinical Insomnia	44 (23.8%)
Subthreshold Clinical Insomnia	63 (34.1%)
Not Clinical Significant	57 (30.8%)
OQ-45 Total Severity² (nmiss = 2)	
Significant	83 (44.6%)
Not Significant	103 (55.4%)
OQ-45 Symptom Distress Severity³ (nmiss = 2)	
Significant	78 (41.9%)
Not Significant	108 (58.1%)
OQ-45 Interpersonal Relations Severity⁴ (nmiss = 2)	
Significant	108 (58.1%)
Not Significant	78 (41.9%)
OQ-45 Social Role Severity⁵ (nmiss = 2)	
Significant	69 (37.1%)
Not Significant	117 (62.9%)



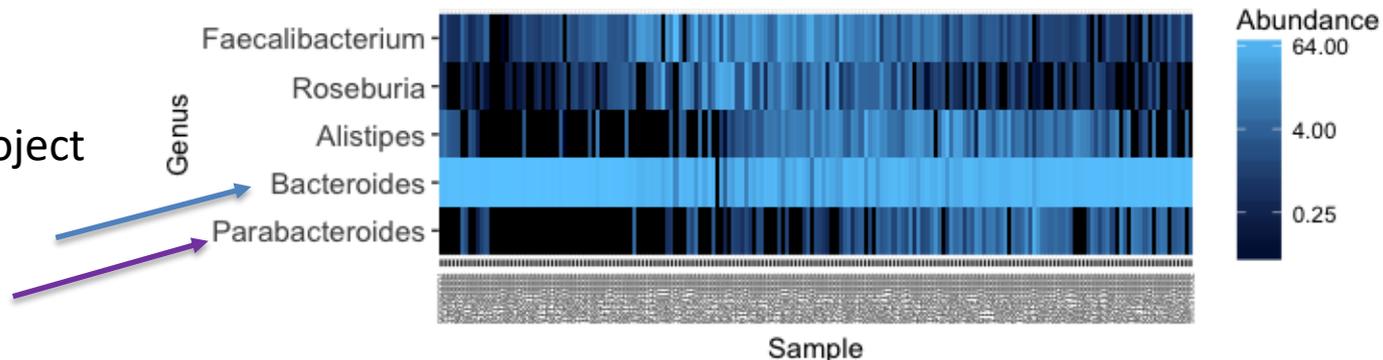
Veteran Microbiome Project - Stool, Skin, & Oral Samples – Weighted Unifrac



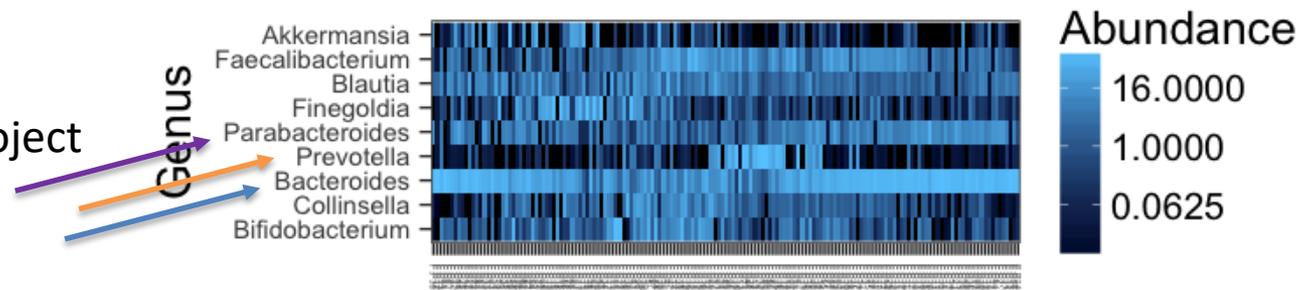


Stool Genus – Top 20 OTUs

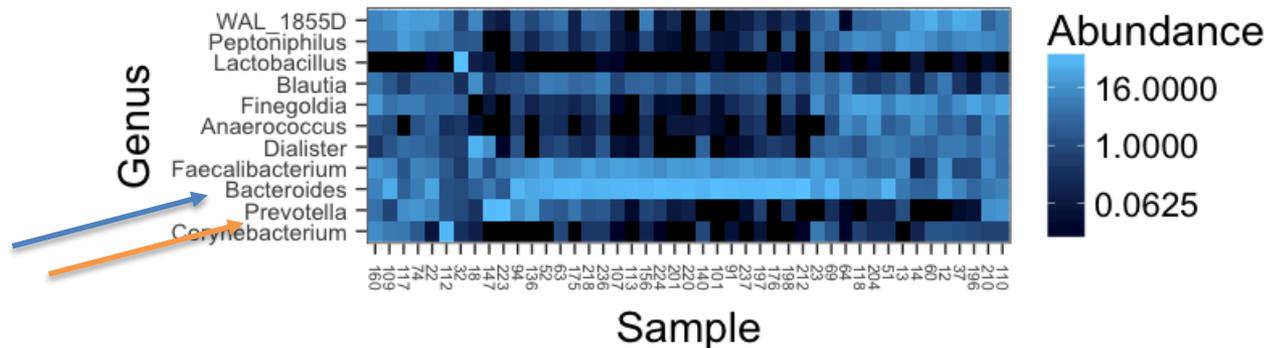
Human Microbiome Project



Veteran Microbiome Project

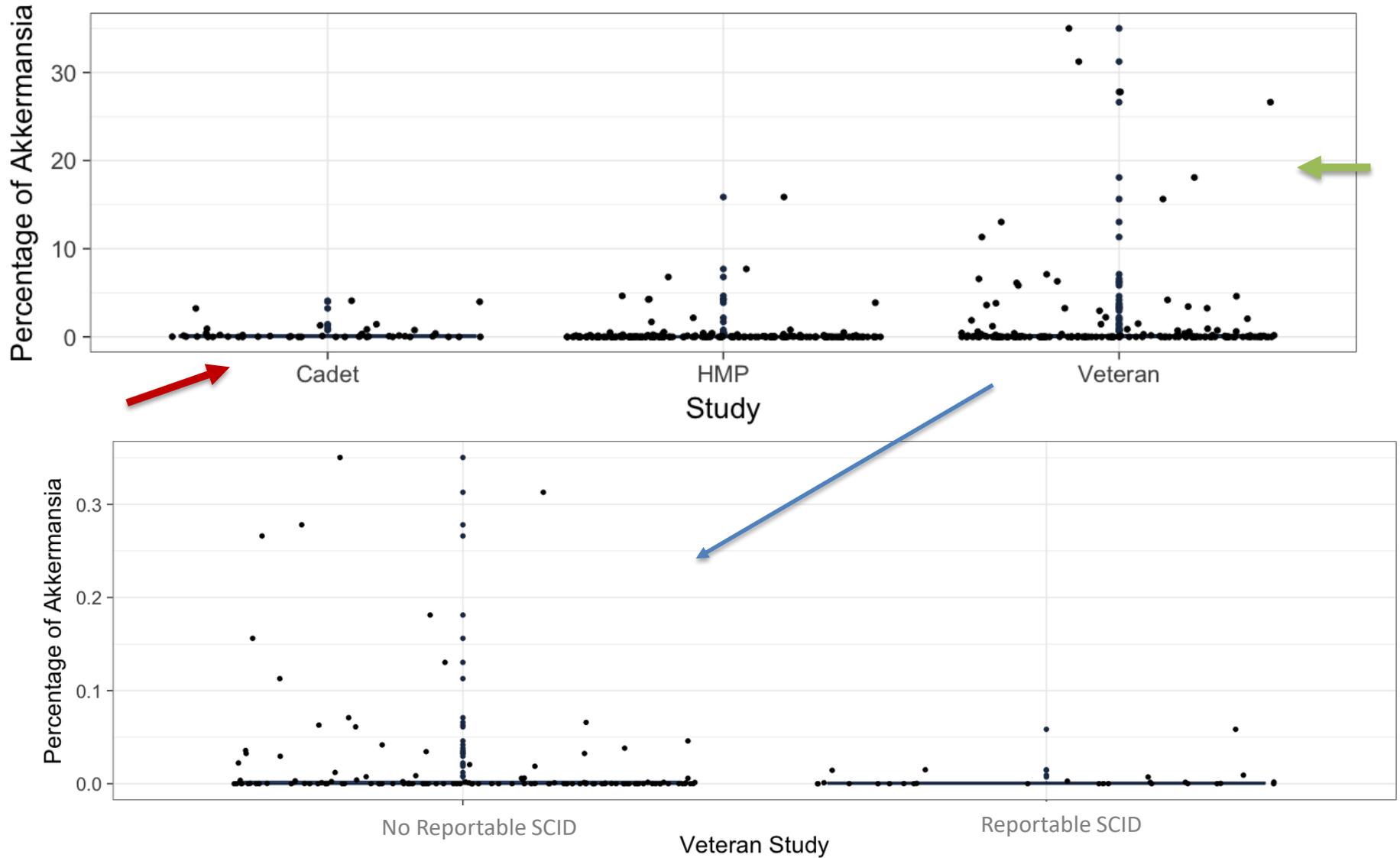


Cadet Microbiome Project



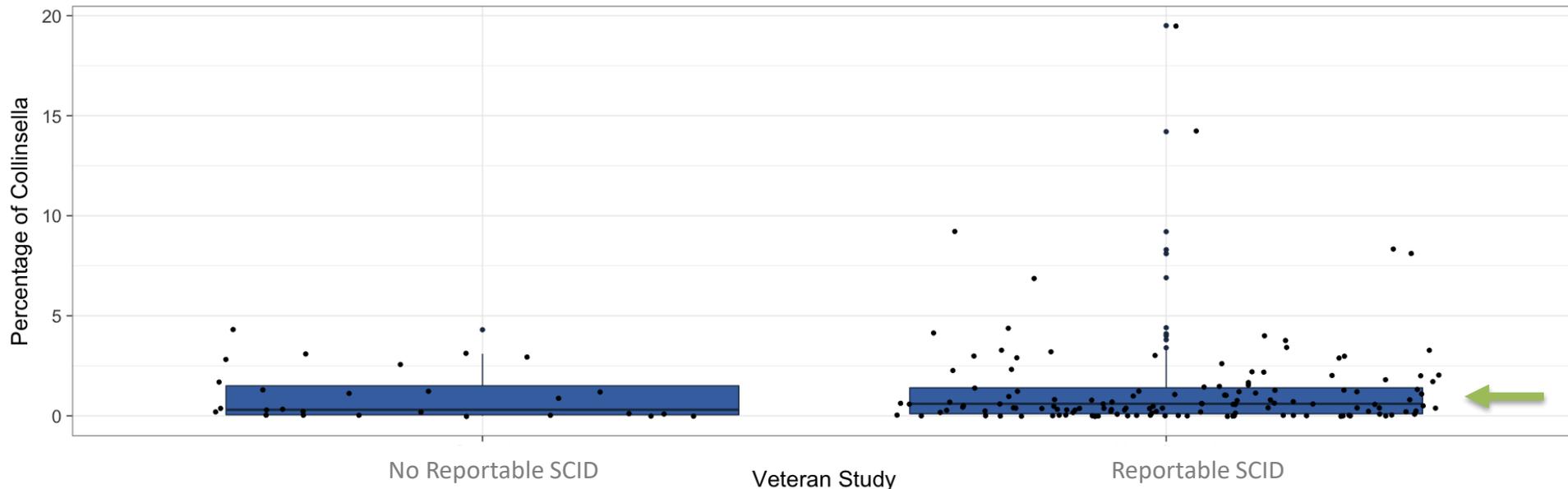


Veteran Microbiome Study – *Genus Akkermansia*





Veteran Microbiome Study – Genus *Collinsella*



Chen *et al. Genome Medicine* (2016) 8:43
DOI 10.1186/s13073-016-0299-7

Genome Medicine

RESEARCH

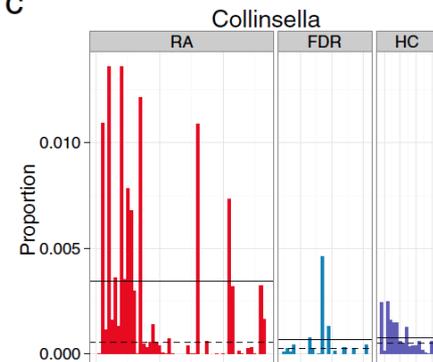
Open Access

An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis

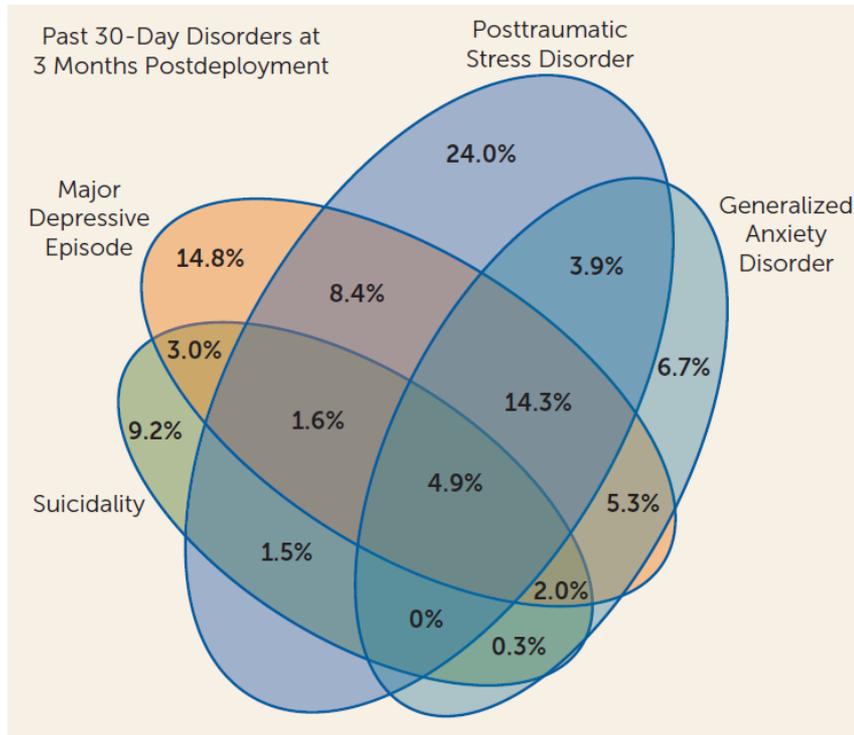
Jun Chen¹, Kerry Wright^{2†}, John M. Davis^{2†}, Patricio Jeraldo⁴, Eric V. Marietta³, Joseph Murray³, Heidi Nelson⁴, Eric L. Matteson² and Veena Taneja^{5*}



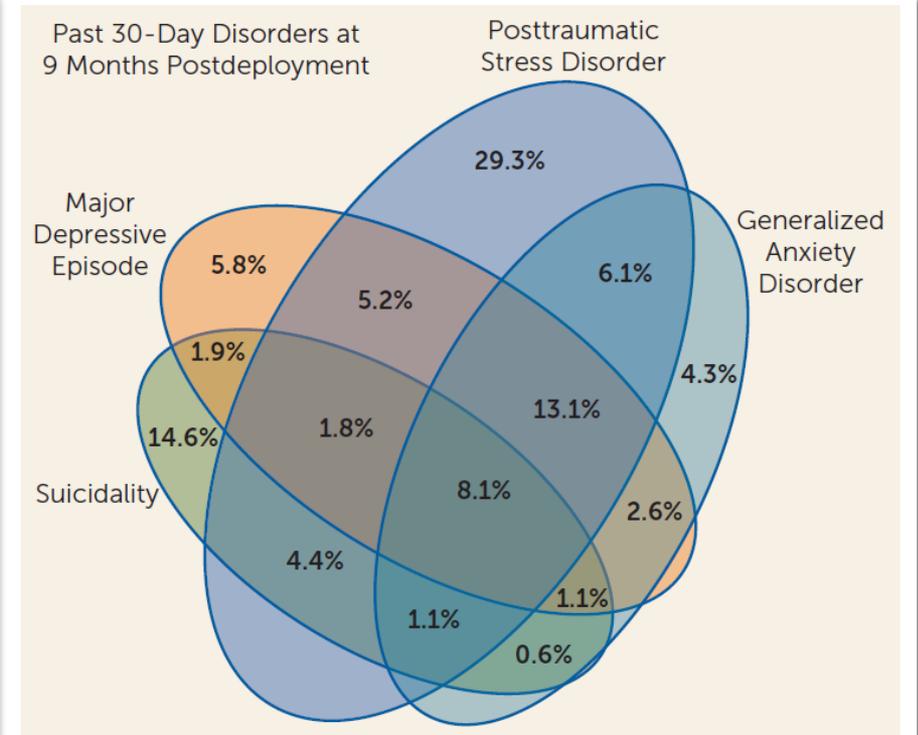
C



TBI is Associated with Increased PTSD Sx



^a Prevalence of any of these four outcomes at T2 was 12.9%.



^a Prevalence of any of these four outcomes at T3 was 16.8%.

Meta-analysis Reveals Transdiagnostic association of Trauma Exposure with Pro-Inflammatory Activity

	<i>k</i>	Total <i>N</i>	Tests of Heterogeneity		Mean <i>r</i>	95% C.I.		<i>p</i>	
			<i>Q</i>	<i>I</i> ²		Lower	Upper		
Acute Phase Proteins									
CRP	16	13 374	1200.8312 [‡]	99.98%	.2507	.0854	.4159	.0030	
Fibrinogen	4	1890	9.6126 [*]	90.26%	.0675	-.0325	.1659	.1860	
Proinflammatory Cytokines									
IL-1 β	4	304	17.1445 [†]	96.94%	.3169	.0269	.6070	.0322	
IL-2	4	362	56.0579 [‡]	99.71%	.3627	-.1015	.8269	.1256	
IL-6	26	7 295	382.5809 [‡]	93.47%	.3029	.1974	.4084	< .0001	
IL-8	5	349	144.6798 [‡]	99.92%	.4649	-.1851	1.1148	.1609	
TNF- α	11	1 899	228.8252 [‡]	99.85%	.2998	.0310	.5687	.0288	

-1.0 -0.5 0.0 0.5 1.0

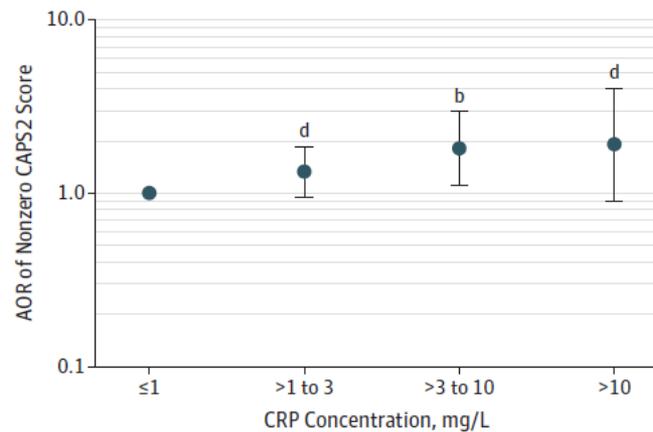
* $p \leq .05$, [†] $p \leq .001$, [‡] $p \leq .0001$

k = Number of studies included in analysis; Total *N* = total number of participants

Tursich et al., 2014, *Transl Psychiatry*, e413:
doi:10.1038/tp.2014.56

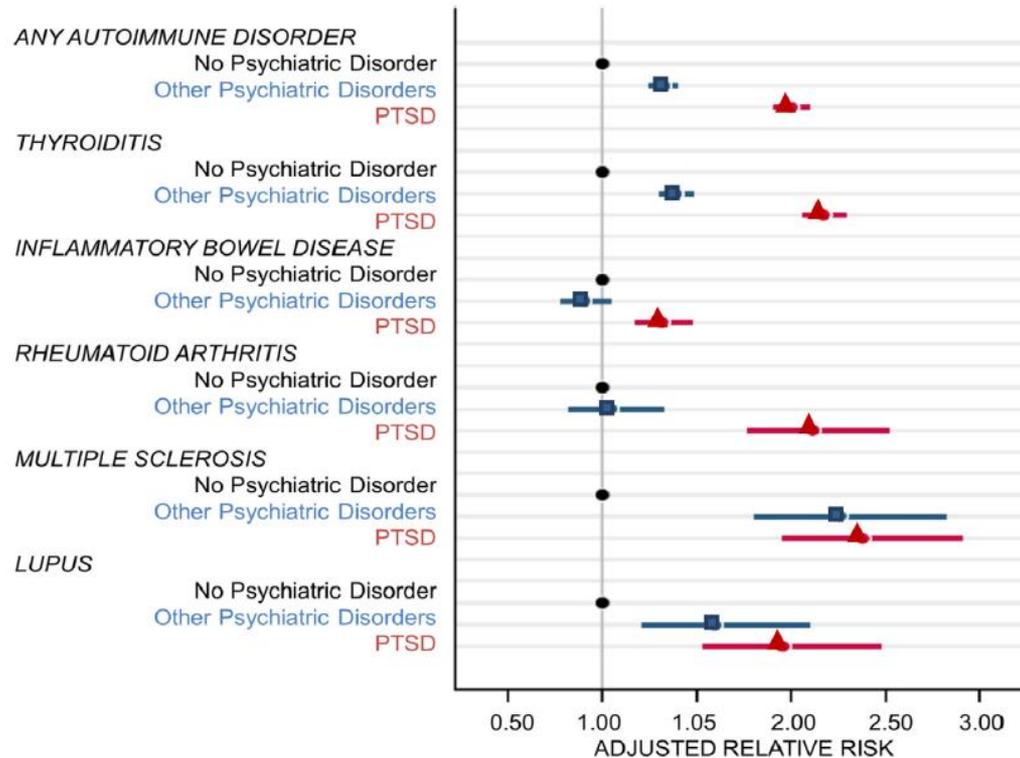
Plasma CRP concentrations before Deployment predict Clinician-Administered PTSD Scale (CAPS) scores ~3 and 6 months Following Deployment

The Marine Resiliency Study, a prospective study of approximately 2600 war zone–deployed Marines



“Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, we found baseline plasma CRP concentration to be a highly significant overall predictor of post-deployment CAPS scores ($p = 0.002$)”

Evidence of Inadequate Immunoregulation in PTSD: Increased Risk of Autoimmune Disorders



O'Donovan et al., 2015, *Biol Psychiatry* 77: 365-374



The Microbiome in Posttraumatic Stress Disorder and Trauma-Exposed Controls: An Exploratory Study

Sian M.J. Hemmings, PhD, Stefanie Malan-Müller, PhD, Leigh L. van den Heuvel, MMed (Psych), Brittany A. Demmitt, PhD, Maggie A. Stanislawski, PhD, David G. Smith, BS, Adam D. Bohr, PhD, Christopher E. Stamper, MS, Embriette R. Hyde, PhD, James T. Morton, BS, Clarisse A. Marotz, MS, Philip H. Siebler, BS, Maarten Braspenning, Ir, Wim Van Criekinge, PhD, Ir, Andrew J. Hoisington, PhD, Lisa A. Brenner, PhD, Teodor T. Postolache, MD, Matthew B. McQueen, ScD, Kenneth S. Krauter, PhD, Rob Knight, PhD, Soraya Seedat, MD, PhD, and Christopher A. Lowry, PhD

Psychosomatic Medicine, V 79 • 936-946 October 2017

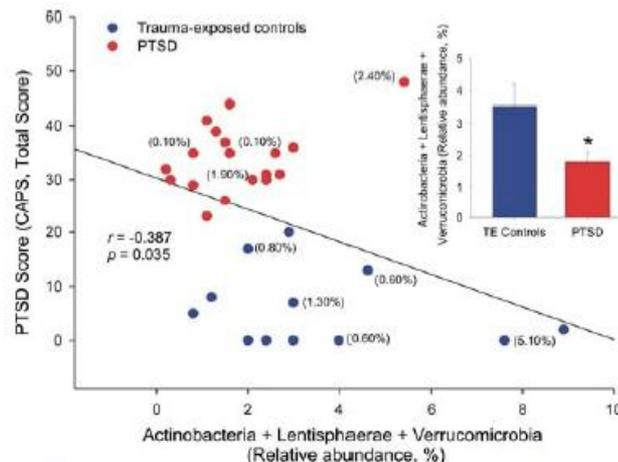
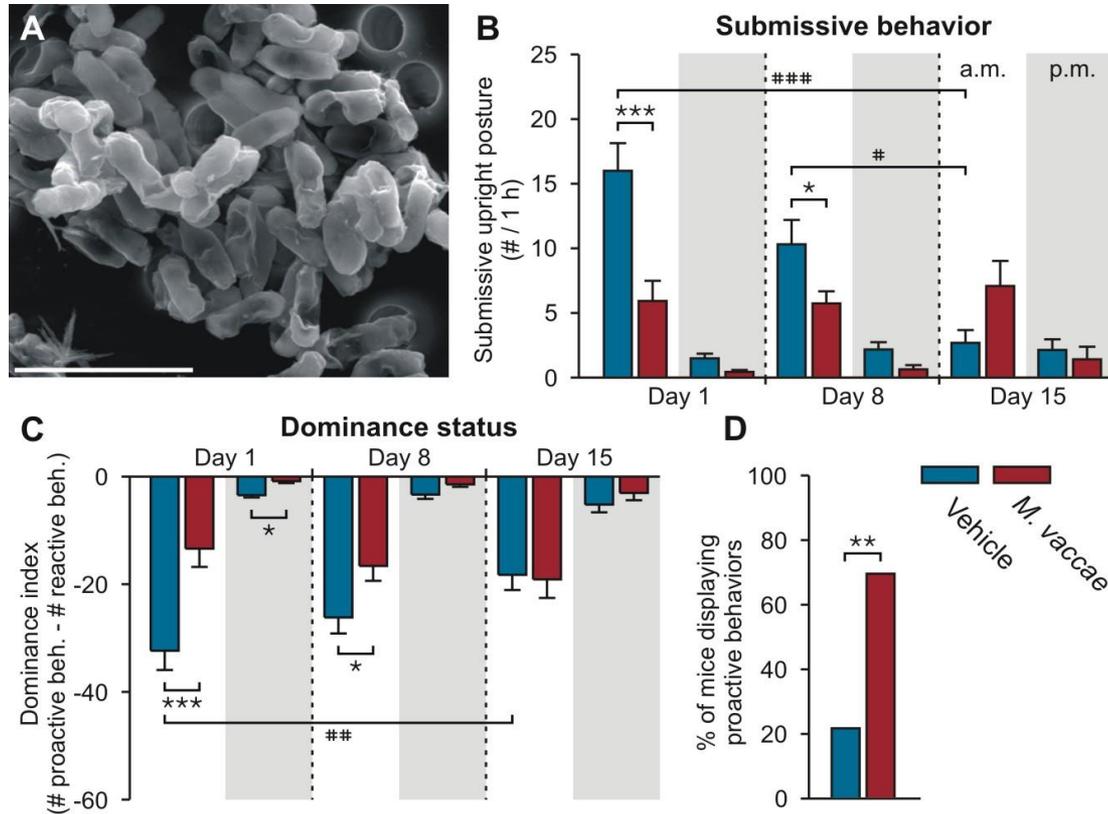


FIGURE 4. Relationship between the random forests interpretation model, relative abundance of [Actinobacteria, Lentisphaerae, Verrucomicrobia] and PTSD scores (CAPS total score). PTSD was negatively correlated with the relative abundance of Actinobacteria, Lentisphaerae, and Verrucomicrobia phyla. In other words, PTSD diagnosis was associated with a decreased abundance of these phyla (Pearson $r = -0.387$; $p = .035$). Percentages in parentheses indicate the percent relative abundance of *Akkermansia*; *Akkermansia* was below the threshold of detection for all other participants. Sample sizes: PTSD participants, $n = 18$; TE controls, $n = 12$. * $p < .05$, Student's t -test. PTSD = posttraumatic stress disorder; CAPS = Clinician-Administered Posttraumatic Stress Disorder Scale for DSM-5; TE = trauma-exposed. Color image is available only in online version (www.psychosomaticmedicine.org).

“The relative abundance of [Actinobacteria, Verrucomicrobia] was also associated with childhood trauma scores (CTQ, total score), with higher CTQ scores associated with lower total relative abundance.”

Immunization with *M. vaccae* Induces a More Proactive Coping Response to Stress





A Systematic Review regarding Prebiotic and Probiotic Interventions for those with Traumatic Brain Injury and/or Posttraumatic Stress Disorder

Population: Adult humans with TBI of any severity, and/or PTSD.

Intervention: Not required for inclusion.

Comparator: Not required for inclusion.

Outcome: All health-related and use-related outcomes. Health-related outcomes include symptom improvement, safety, and adverse events. Use-related outcomes include adherence, duration, and frequency.

Timing/Setting: Restrictions were not based on timing, setting, or study design.



“Only 4 studies were identified (3 severe TBI, 1 PTSD, 0 co-occurring TBI and PTSD). Although findings suggested some promise, work in this area is nascent and results to date do not support some claims within the extensive coverage of probiotics in the popular press.”

Characteristics of Included Studies

Source	Study Design	Setting	Sample	Intervention	Prebiotic/Probiotic	Risk of Bias
Tan et al, 2011	RCT	ICU at Affiliated Hospital of North Sichuan Medical College (China)	N=52; Closed head injury alone	Enteral nutrition within 48 hours of admission.	0.5×10^8 <i>Bifidobacterium longum</i> , 0.5×10^7 <i>Streptococcus thermophilus</i> .	Low
Falcão de Arruda & de Aguiar-Nascimento, 2004	RCT	ICU at the Júlio Muller University Hospital (Brazil)	N=23; Victims of brain injury alone	Standard diet or glutamine-and probiotics-enriched diet.	<i>Lactobacillus johnsonii</i> .	High
Gocan et al, 2012	Before and after study	Military Hospital, Victor Babes, (Romania)	N=11; PTSD	All participants consumed a specially formulated fermented soy product daily.	120 mL FSWW08 (fermented soy)	High
Painter et al., 2015	Retrospective cohort	Cedars-Sinai Medical Center (CA)	N=240; severely brain injured	Registry was queried for patients who received SF or an IEN formula based on surgeon's preference.	The SF was a Two-cal formula or similar formula. The IEN formula was Pivot-1.5.	High

VA



U.S. Department
of Veterans Affairs



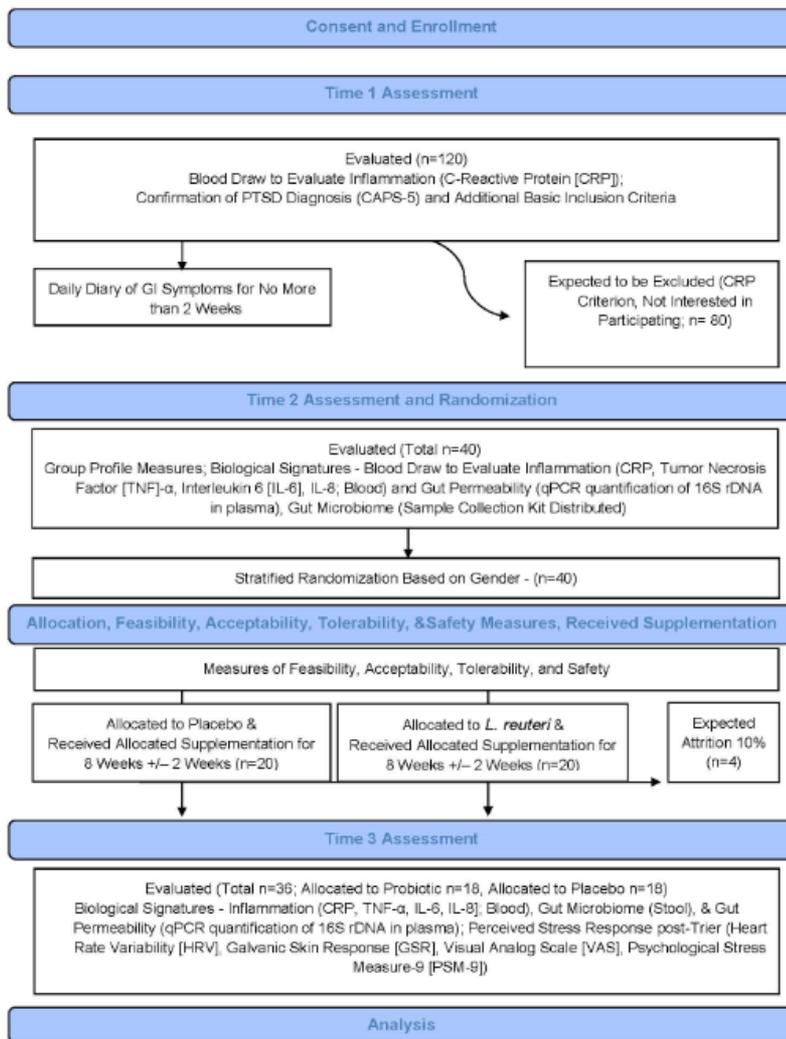
VHA SPIRE GRANT – RR&D

Biological Signature and Safety of an Immunomodulatory Probiotic Intervention for Veterans with Co-Occurring Mild TBI and PTSD

1 I21 RX002232-01

Lisa A. Brenner, Ph.D., Principal Investigator, **Christopher A. Lowry, Ph.D.,** Co-I, **LtCol Andrew J. Hoisington, Ph.D., PE,** Kerry Kinney, Co-I, **Jeri E. Forster, Ph.D.,** **Stephen D. Bartlett, R.Ph., M.S.P.H.,** Co-I, **Teodor T. Postolache, M.D.,** Co-I







Conclusions

- Exposure to immunoregulatory “Old Friends” has declined dramatically in developed countries in the last 50 years
- Negative outcomes post-TBI and psychiatric disorders are associated with decreased immunoregulation, and increased inflammation
- Immunization with *M. vaccae* prevents stress-induced inflammation and anxiety/fear
- Interventions to increase anti-inflammatory/ immunoregulatory signaling might be considered for prevention and treatment post-TBI, psychiatric conditions, and co-occurring disorders



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@LisaABrenner

Military and Veteran Microbiome: Consortium for Research and Education

MISSION: Advancing microbiome science and education to benefit military personnel, Veterans, and their families.

<https://www.mirecc.va.gov/visn19/mvm/>



Alfred P. Sloan Foundation