GULF WAR ILLNESS

Using a Consensus Docking Approach to Predict Adverse Drug Reactions in Combination Drug Therapies for Gulf War Illness.
Jaundoo R1,2,3, Bohmann J4, Gutierrez GE5, Klimas N6,7,8, Broderick G9,10,11,12,13, Craddock TJA14,15,16,17.

Gulf War Illness (GWI) is a chronic multisymptom illness characterized by fatigue, musculoskeletal pain, and gastrointestinal and cognitive dysfunction believed to stem from chemical exposures during the 1990–1991 Persian Gulf War. There are currently no treatments; however, previous studies have predicted a putative multi-intervention treatment composed of inhibiting Th1 immune cytokines followed by inhibition of the glucocorticoid receptor (GCR) to treat GWI. These predictions suggest the use of specific monoclonal antibodies or suramin to target interleukin-2 and tumor necrosis factor α, followed by mifepristone to inhibit the GCR. In addition to this putative treatment strategy, there exist a variety of medications that target GWI symptomatology. As pharmaceuticals are promiscuous molecules, binding to multiple sites beyond their intended targets, leading to off-target interactions, it is key to ensure that none of these medications interfere with the proposed treatment avenue. Here, we used the drug docking programs AutoDock 4.2, AutoDock Vina, and Schrödinger's Glide to assess the potential off-target immune and hormone interactions of 43 FDA-approved drugs commonly used to treat GWI symptoms in order to determine their putative polypharmacology and minimize adverse drug effects in a combined pharmaceutical treatment. Several of these FDA-approved drugs were predicted to be novel binders of immune and hormonal targets, suggesting caution for their use in the proposed GWI treatment strategy symptoms.

CHRONIC FATIGUE SYNDROME

The development of an instrument to assess post-exertional malaise in patients with myalgic encephalomyelitis and chronic fatigue syndrome.
Jason LA1, Holtzman CS1, Sunnquist M1, Cotler J1.

Post-exertional malaise, or a variation of this term, is a key symptom of myalgic encephalomyelitis and chronic fatigue syndrome, as this symptom is mentioned in almost all myalgic encephalomyelitis and chronic fatigue syndrome case definitions. Until now there has not been a comprehensive questionnaire to assess post-exertional malaise. To rectify this situation, in this article we describe the development of a new questionnaire, called the DePaul Post-Exertional Malaise Questionnaire, which was based on input from hundreds of patients. Preliminary validation was provided by the findings of significant and predictable relationships between different domains of this post-exertional malaise questionnaire and physical functioning.
Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study.

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BACKGROUND: A substantial proportion of patients with migraine does not respond to, or cannot tolerate, oral preventive treatments. Erenumab is a novel CGRP-receptor antibody with preventive efficacy in migraine. We assessed its efficacy and tolerability in patients with episodic migraine in whom previous treatment with two-to-four migraine preventives had been unsuccessful.

METHODS: LIBERTY was a 12-week, double-blind, placebo-controlled randomised study at 59 sites in 16 countries. Eligible patients were aged 18-65 years and had a history of episodic migraine with or without aura for at least 12 months, had migraine for an average of 4-14 days per month during the 3 months before screening, and had been treated unsuccessfully (in terms of either efficacy or tolerability, or both) with between two and four preventive treatments. Eligible participants were randomly assigned (1:1) to receive either erenumab 140 mg (via two 70 mg injections) or placebo every 4 weeks subcutaneously for 12 weeks. Randomisation was by interactive response technology and was stratified by monthly frequency of migraine headache (4-7 vs 8-14 migraine days per month) during the baseline phase. Cenduit generated the randomisation list and assigned participants to groups. Participants, investigators, people doing various assessments, and the study sponsor were masked to treatment assignment. The primary endpoint was the proportion of patients achieving a 50% or greater reduction in the mean number of monthly migraine days during weeks 9-12. Efficacy was measured in the full analysis set, which included all randomly assigned patients who started their assigned treatment and completed at least one post-baseline monthly migraine day measurement. Safety and tolerability were assessed by recording adverse events and by physical examination, assessment of vital signs, clinical laboratory assessments, and electrocardiography. Safety was assessed in all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT03096834. The trial is closed to new participants, but the open-label extension phase is ongoing.

FINDINGS: Between March 20, 2017, and Oct 27, 2017, 246 participants were randomly assigned, 121 to the erenumab group and 125 to the placebo group. 95 of 246 (39%) participants had previously unsuccessfully tried two preventive drugs, 93 (38%) had tried three, and 56 (23%) had tried four. At week 12, 36 (30%) patients in the erenumab had a 50% or greater reduction from baseline in the mean number of monthly migraine days during weeks 9-12. Efficacy was measured in the full analysis set, which included all randomly assigned patients who started their assigned treatment and completed at least one post-baseline monthly migraine day measurement. Safety and tolerability were assessed by recording adverse events and by physical examination, assessment of vital signs, clinical laboratory assessments, and electrocardiography. Safety was assessed in all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT03096834. The trial is closed to new participants, but the open-label extension phase is ongoing.

INTERPRETATION: Compared with placebo, erenumab was efficacious in patients with episodic migraine who previously did not respond to or tolerate between two and four previous migraine preventive treatments. Erenumab might be an option for patients with difficult-to-treat migraine who have high unmet needs and few treatment options.
HEADACHE and MIGRAINE (Continued)

Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016.

GBD 2016 Headache Collaborators. Collaborators (53)

BACKGROUND: Through the Global Burden of Diseases, Injuries, and Risk Factors (GBD) studies, headache has emerged as a major global public health concern. We aimed to use data from the GBD 2016 study to provide new estimates for prevalence and years of life lived with disability (YLDs) for migraine and tension-type headache and to present the methods and results in an accessible way for clinicians and researchers of headache disorders.

METHODS: Data were derived from population-based cross-sectional surveys on migraine and tension-type headache. Prevalence for each sex and 5-year age group interval (ie, age 5 years to ≥95 years) at different time points from 1990 and 2016 in all countries and GBD regions were estimated using a Bayesian meta-regression model. Disease burden measured in YLDs was calculated from prevalence and average time spent with headache multiplied by disability weights (a measure of the relative severity of the disabling consequence of a disease). The burden stemming from medication overuse headache, which was included in earlier iterations of GBD as a separate cause, was subsumed as a sequela of either migraine or tension-type headache. Because no deaths were assigned to headaches as the underlying cause, YLDs equate to disability-adjusted life-years (DALYs). We also analysed results on the basis of the Socio-demographic Index (SDI), a compound measure of income per capita, education, and fertility.

FINDINGS: Almost three billion individuals were estimated to have a migraine or tension-type headache in 2016: 1·89 billion (95% uncertainty interval [UI] 1·71-2·10) with tension-type headache and 1·04 billion (95% UI 1·00-1·09) with migraine. However, because migraine had a much higher disability weight than tension-type headache, migraine caused 45·1 million (95% UI 29·0-62·8) and tension-type headache only 7·2 million (95% UI 4·6-10·5) YLDs globally in 2016. The headaches were most burdensome in women between ages 15 and 49 years, with migraine causing 20·3 million (95% UI 12·9-28·5) and tension-type headache 2·9 million (95% UI 1·8-4·2) YLDs in 2016, which was 11·2% of all YLDs in this age group and sex. Age-standardised DALYs for each headache type showed a small increase as SDI increased.

INTERPRETATION: Although current estimates are based on limited data, our study shows that headache disorders, and migraine in particular, are important causes of disability worldwide, and deserve greater attention in health policy debates and research resource allocation. Future iterations of this study, based on sources from additional countries and with less methodological heterogeneity, should help to provide stronger evidence of the need for action.

FUNDING: Bill & Melinda Gates Foundation.

Painful Craniofacial/Cervical Surface Area and Continuous Headache After Military Concussion: A Morphometric Retrospective Cohort Study.

Klaric JS1, Forbes LL2, Finkel AG1,3,4.

OBJECTIVE: In this retrospective study of active duty service members (ADSMs), possible relationships were examined between extent of headache pain depicted on head/neck diagrams and headache phenomenology.

BACKGROUND: The signature injury of US military operations in Iraq and Afghanistan is mild traumatic brain injury (mTBI). Blast injury, especially from improvised explosive devices, was the most common cause during the height of the wars; the most persistent symptom remains posttraumatic headache (PTH). Neurologic patients were asked to draw pain diagrams/maps, a method of pain assessment in several clinical settings.

METHODS: Thirty-four ADSMs attributing PTH to both blast and non-blast sources underwent clinical evaluations; diagnoses and headache characteristics were obtained. They completed 58 drawings depicting craniofacial/cervical headache pain on non-standardized templates. Drawings were of 29 continuous and 29 non-continuous headaches (CHA and NCHA, respectively). Surface area was calculated using a grid and expressed as a percentage.

RESULTS: The sample was male (100%), primarily white (83%), with an average age of 30.3 years. Evidence for statistical independence of observations is provided (intra-class correlation = 0.004). Percent surface area was larger for CHA (median [mdn] = 35.2, interquartile range [IQR] = 9.0, 78.3) than NCHA (mdn = 9.1, IQR = 5.4, 34.1, P = .029). In those with blast injury, CHA percent surface areas (mdn = 45.9, IQR = 27.0, 100) were larger than NCHA (mdn = 11.6, IQR = 5.8, 28.9; P = .0012), a relationship not observed in patients with PTH from non-blasts (CHA: mdn = 26.8, IQR = 8.5, 52.0; NCHA: mdn = 9.1, IQR = 5.0, 47.6, P = .050). This pattern is observed after pooling at the median (blast, P < .012; non-blast: P = .264).

CONCLUSION: Painful craniofacial/cervical surface area, as shown on patient drawings, is related to PTH phenomenology (continuous versus non-continuous headache). This relationship is stronger after blast injury.
HEADACHE and MIGRAINE (Continued)

**Improving Medical Communication in Migraine Management: A Modified Delphi Study to Develop a Digital Migraine Tracker.**

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**OBJECTIVE:** This study aimed to identify the essential content and amount of information to be collected from people with migraine via a patient-facing smartphone-based migraine tracker for them to share with clinicians during live discussions to assist in optimizing migraine management. The proposed tracker is intended for use in non-interventional research to evaluate disease burden in episodic migraine and chronic migraine patients as assessed by demographic and clinical characteristics and health resource utilization in an integrated delivery network setting. The proposed tracker is not intended for commercial purposes.

**BACKGROUND:** Epidemiological studies suggest migraine is underdiagnosed and undertreated. Studies of patient-clinician interactions suggest that effective medical communication may help address these issues.

**METHODS:** Four migraine practice leaders, an epidemiologist with extensive migraine experience, and a measurement expert took part in a modified Delphi panel process to identify data elements that could be collected from people with migraine through a smartphone-based migraine tracker. Importantly, the proposed tracker would not be intended to replace the patient-clinician encounter but to support the encounter through enabling the patient to document migraine symptoms and experiences in a timely and accurate manner for sharing with a clinician as part of a broader face-to-face discussion. The panel reviewed questions derived from the existing migraine diaries in the public domain, those used in clinical trials, and patient-centric surveys assessing the impact of migraine on physical function and other related concepts. Key considerations included identification of the most clinically useful data elements for a shared communication tool for people with migraine under the care of a clinician. The panel also identified numerous functionality requirements for such a tool and provided recommendations on the most effective way to present results to a clinician.

**RESULTS:** The expert panel opined that people with migraine may value the ability to capture a relatively broad range of information for their own migraine-tracking purposes, while clinicians will likely find greater value in a small set of data relevant to the management of migraine. The panel identified the 3 most essential concepts in categories of data for a clinician, for which they coined the term "The 3 Fs": Frequency of days with headache; Frequency of acute medication usage; and Functional impairment. Information on the frequency of days with headache was felt to combine with the information on the frequency of acute medication usage to provide essential insights into current migraine management strategy and its outcomes, and to assist considerations of preventive measures. Functional impairment was treated as an effective surrogate for headache severity and was assessed based on the following: degree of difficulty in performing activities of daily living, impact on absenteeism (taking leave from work or cancelling/avoiding other activities) and presenteeism (performing work or other daily activities, with reduced productivity/capability), and amount of rest required as a result of a migraine attack. The modified Delphi panel process resulted in the selection of 13 questions in 8 categories to elicit sufficient and meaningful data comprising headache occurrence, symptoms, daily/preventive and as-needed/acute medication usage, triggers, ability to concentrate, and functional impairment. The panel also agreed that the tracker should generate 2 distinct reports: one for people with migraine that would include a wider range of data about symptoms and perceived triggers, and a targeted report for the clinician that would place prime emphasis on the 3 Fs for aggregating the results of each headache occurrence and the trend over time.

**CONCLUSIONS:** A system that easily captures critical data elements about migraine, with specific feedback displays for patients to share with clinicians during live discussions, may offer some benefit to people with migraine and their clinicians by facilitating more objective communication and optimizing management. The tracker’s output may enable people with migraine to track a wide range of data for their own purposes, allowing them to better understand their condition, while a synthesized view of the selected data may support more informed clinical decision-making for the clinician and individualized, evidence-based discussion with the patient. As a result, this shared decision-making tool may enable patients to more accurately convey essential migraine information during live patient-­clinician discussions to drive improved management and patient outcomes.
What is the effect of alcohol consumption on the risk of chronic widespread pain? A Mendelian randomisation study using UK Biobank.

Beasley M1,2, Freidin MB3, Basu N1,2, Williams FMK3, Macfarlane GJ1,2.

Studies have shown that moderate alcohol consumption is strongly associated with reduced reporting of chronic widespread pain (CWP). The study designs used however are prone to confounding and are not able to establish the direction of causality. The current study overcomes these problems by using the Mendelian randomisation design to determine the effect of alcohol consumption on the likelihood of reporting CWP. The UK Biobank recruited 500,000 participants aged between 40 and 69 years. Data collected included questions on chronic pain and alcohol consumption, and biological samples providing genotypic information. Alcohol consumption was categorised as 'weekly consumption' or 'non or infrequent'. Participants were classified by genotype according to alleles of the rs1229984 SNP, either 'GG' or 'AA/AG'. CWP was defined as pain all over the body for more than 3 months that interfered with activities. Associations between genotype, CWP and alcohol consumption were tested by logistic regression. Instrumental variable analysis was used to calculate the causal effect of weekly alcohol consumption on CWP. Persons with 'GG' genotype had an increased risk of CWP (odds ratio, OR 1.17, 99% confidence interval CI 1.01-1.35) and were more likely to consume alcohol weekly (OR 1.76, 1.70-1.81) compared to those with 'AA/AG' genotype. Weekly consumption of alcohol was associated with reduced risk of CWP (OR 0.33, 0.31-0.35), but instrumental variable analysis did not show a causal effect of alcohol consumption on reducing CWP (OR 1.29, 0.96-1.74). An interpretation of observational population studies as showing a protective effect of alcohol on CWP is not supported.

Prognostic Factors for Physical Functioning After Multidisciplinary Rehabilitation in Patients with Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis.

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OBJECTIVES: This systematic review aimed to identify and evaluate prognostic factors for long-term (≥6 mo) physical functioning in patients with chronic musculoskeletal pain following multidisciplinary rehabilitation (MDR).

METHODS: Electronic searches conducted in MEDLINE, PsycINFO, EMBASE, CINAHL, Web of Science, and Cochrane CENTRAL revealed 25 original research reports, published 1983-2016, (n=9436). Potential prognostic factors relating to initial pain and physical and psychological functioning were synthesized qualitatively and quantitatively in random effects meta-analyses. The level of evidence (LoE) was evaluated with GRADE.

RESULTS: Pain related factors (intensity and chronicity) were not associated with function/disability at long-term follow up, OR=0.84, 95% CI: 0.65-1.07 and OR=0.97, 95% CI: 0.93-1.00 respectively (moderate LoE). A better function at follow up was predicted by Physical factors; higher levels of initial self-reported functioning, OR=1.07, 95% CI: 1.02-1.13 (low LoE), and Psychological factors; low initial levels of emotional distress, OR=0.77, 95% CI: 0.65-0.92, low levels of cognitive behavioural risk factors, OR 0.85, 95% CI: 0.77-0.93 and high levels of protective cognitive behavioural factors, OR=1.49; 95% CI: 1.17-1.90 (moderate LoE).

DISCUSSION: While pain intensity and long-term chronicity did not predict physical functioning in chronic pain patients after MDR, poor pre-treatment physical and psychological functioning influenced the prognosis negatively. Thus, treatment should further target and optimize these modifiable factors and an increased focus on positive, psychological protective factors may perhaps provide an opening for yet untapped clinical gains.
The effects of walking intervention in patients with chronic low back pain: A meta-analysis of randomized controlled trials.
Sitthipornvorakul E1, Klinsophon T2, Sihawong R2, Janwantanakul P3.

OBJECTIVE: The aim of this meta-analysis of randomized controlled trials was to gain insight into the effectiveness of walking intervention on pain, disability, and quality of life in patients with chronic low back pain (LBP) at post intervention and follow ups.

METHOD: Six electronic databases (PubMed, Science Direct, Web of Science, Scopus, PEDro and The Cochrane library) were searched from 1980 to October 2017. The following keywords were used: Walk* or Pedometer* or Accelerometer* or Treadmill* paired with "Back pain", "Low back pain", "Chronic low back pain", "LBP", or "Backache". Randomized controlled trials in patients with chronic LBP were included if they compared the effects of walking intervention to non-pharmacological interventions. Pain, disability, and quality of life were the primary health outcomes.

RESULTS: Nine studies were suitable for meta-analysis. Data was analyzed according to the duration of follow-up (short-term, < 3 months; intermediate-term, between 3 and 12 months; long-term, > 12 months). Low- to moderate-quality evidence suggests that walking intervention in patients with chronic LBP was as effective as other non-pharmacological interventions on pain and disability reduction in both short- and intermediate-term follow ups.

CONCLUSIONS: Unless supplementary high-quality studies provide different evidence, walking, which is easy to perform and highly accessible, can be recommended in the management of chronic LBP to reduce pain and disability.

OTHER RESEARCH OF INTEREST

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial.
Yesavage JA1,2, Fairchild JK1,2, Mi Z3, Biswas K3, Davis-Karim A4, Phibbs CS5,6, Forman SD7,8, Thase M9, Williams LM1,2, Etkin A1,2,10, O’Hara R1,2, Georgette G1, Beale T1, Huang GD11, Noda A2, George MS12,13; VA Cooperative Studies Program Study Team.

Importance: Treatment-resistant major depression (TRMD) in veterans is a major clinical challenge given the high risk for suicidality in these patients. Repetitive transcranial magnetic stimulation (rTMS) offers the potential for a novel treatment modality for these veterans.

Objective: To determine the efficacy of rTMS in the treatment of TRMD in veterans.

Design, Setting, and Participants: A double-blind, sham-controlled randomized clinical trial was conducted from September 1, 2012, to December 31, 2016, in 9 Veterans Affairs medical centers. A total of 164 veterans with TRD participated.

Interventions: Participants were randomized to either left prefrontal rTMS treatment (10 Hz, 120% motor threshold, 4000 pulses/session) or to sham (control) rTMS treatment for up to 30 treatment sessions.

Main Outcomes and Measures: The primary dependent measure of the intention-to-treat analysis was remission rate (Hamilton Rating Scale for Depression score ≤10, indicating that depression is in remission and not a clinically significant burden), and secondary analyses were conducted on other indices of posttraumatic stress disorder, depression, hopelessness, suicidality, and quality of life.

Results: The 164 participants had a mean (SD) age of 55.2 (12.4) years, 132 (80.5%) were men, and 126 (76.8%) were of white race. Of these, 81 were randomized to receive active rTMS and 83 to receive sham. For the primary analysis of remission, there was no significant effect of treatment (odds ratio, 1.16; 95% CI, 0.59-2.26; $P = .67$). At the end of the acute treatment phase, 33 of 81 (40.7%) of those in the active treatment group achieved remission of depressive symptoms compared with 31 of 83 (37.4%) of those in the sham treatment group. Overall, 64 of 164 (39.0%) of the participants achieved remission.

Conclusions and Relevance: A total of 39.0% of the veterans who participated in this trial experienced clinically significant improvement resulting in remission of depressive symptoms; however, there was no evidence of difference in remission rates between the active and sham treatments. These findings may reflect the importance of close clinical surveillance, rigorous monitoring of concomitant medication, and regular interaction with clinic staff in bringing about significant improvement in this treatment-resistant population.

Trial Registration: ClinicalTrials.gov Identifier: NCT01191333.
OTHER RESEARCH OF INTEREST (Continued)

**The association of Inflammatory Bowel diseases with autoimmune disorders: a population-based report from the epi-IIRN.**

Bar Yehuda S1, Axlerod R1, Toker O2, Zigman N3, Goren I3, Mourad V4, Lederman N4, Cohen N4, Matz E5, Dushnitzky D5, Gavish M6, Borovsky N5, Schwarts D7, Dotan I8, Turner D1.


**Introduction:** There are conflicting data on the association between inflammatory bowel diseases (IBD) and autoimmune disorders. The aim of this study was to explore this association including the effect of medications on this association.

**Methods:** We utilized health administrative data collected by 3 of 4 Israel's Health Maintenance Organizations (HMO) covering 52% of the population of Israel. We explored the prevalence of the following autoimmune disorders: Insulin Dependent Diabetes Mellitus (IDDM), psoriasis, Sjögren syndrome, celiac, systemic lupus erythematosus (SLE), primary sclerosis cholangitis (PSC) and autoimmune thyroiditis, among all IBD patients versus non-IBD controls. Case ascertainment was determined according to validated computerized algorithms.

**Results:** 12,625 IBD patients were compared to 12,625 controls. A total of 1,395 (11.1%) IBD patients had at least one autoimmune disease compared with 740 (5.9%) of non-IBD controls (OR 95%CI=1.99 (1.81-2.19); P<0.05); all autoimmune diseases, except for thyroiditis, were more prevalent among IBD patients. Adjusted for confounding variables, anti-TNF medications were associated with a higher prevalence of psoriasis (54 (5.7%) in IBD vs 177 (4.1%) in controls; OR 95%CI=1.50 (1.07-2.08); P<0.05) but lower prevalence of Sjögren (1 (0.1%) vs. 39 (0.9%); OR 95%CI=0.13 (0.02-0.94); P<0.05) and celiac disease (11 (1.2%) vs. 68 (1.6%); OR 95%CI=0.51 (0.27-0.99); P<0.05). Thiopurines and 5ASA were not associated with any autoimmune disorder.

**Conclusion:** IBD is associated with all autoimmune diseases explored here except for thyroiditis. Anti-TNF users have a higher prevalence of psoriasis, and lower prevalence of Sjögren and celiac disease.

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**Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features.**

Zmora N1, Zilberman-Schapira G2, Suez J3, Mor U2, Dori-Bachash M2, Bashardes S2, Kotler E3, Zur M2, Regev-Lehavi D2, Brik RB2, Federici S2, Cohen Y2, Linevsky R2, Rothschild D3, Moor AE4, Ben-Moshe S4, Harmelin A5, Itzkovitz S4, Maharshak N6, Shibolet O6, Shapiro H2, Pevsner-Fischer M2, Sharon I7, Halpern Z8, Segal E9, Elinav E10.


Empiric probiotics are commonly consumed by healthy individuals as means of life quality improvement and disease prevention. However, evidence of probiotic gut mucosal colonization efficacy remains sparse and controversial. We metagenomically characterized the murine and human mucosal-associated gastrointestinal microbiome and found it to only partially correlate with stool microbiome. A sequential invasive multi-omics measurement at baseline and during consumption of an 11-strain probiotic combination or placebo demonstrated that probiotics remain viable upon gastrointestinal passage. In colonized, but not germ-free mice, probiotics encountered a marked mucosal colonization resistance. In contrast, humans featured person-, region- and strain-specific mucosal colonization patterns, hallmarked by predictive baseline host and microbiome features, but indistinguishable by probiotics presence in stool. Consequently, probiotics induced a transient, individualized impact on mucosal community structure and gut transcriptome. Collectively, empiric probiotics supplementation may be limited in universally and persistently impacting the gut mucosa, meriting development of new personalized probiotic approaches.

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