GULF WAR ILLNESS

Inhibition of microRNA-124-3p as a novel therapeutic strategy for the treatment of Gulf War Illness: evaluation in a rat model.

Laferriere NR[1], Kurata WE[2], Grayson CT 3rd[1], Stecklow KM[2], Pierce LM[3].

Neurotoxicology. **2018 Nov 29**. pii: S0161-813X(18)30319-X. doi: 10.1016/j.neuro.2018.11.008. PMID: 30503814. [Epub ahead of print]

Gulf War Illness (GWI) is a chronic, multisymptom illness that continues to affect up to 30% of veterans deployed to the Persian Gulf during the 1990-1991 Gulf War. After nearly 30 years, useful treatments for GWI are lacking and underlying cellular and molecular mechanisms involved in its pathobiology remain poorly understood, although exposures to pyridostigmine bromide (PB) and pesticides are consistently identified to be among the strongest risk factors. Alleviation of the broad range of symptoms manifested in GWI, which involve the central nervous system, the neuroendocrine system, and the immune system likely requires therapies that are able to activate and inactivate a large set of orchestrated genes. Previous work in our laboratory using an established rat model of GWI identified persistent elevation of microRNA-124-3p (miR-124) levels in the hippocampus whose numerous gene targets are involved in cognition-associated pathways and neuroendocrine function. This study aimed to investigate the broad effects of miR-124 inhibition in the brain 9 months after completion of a 28-day exposure regimen of PB, DEET (N,N-diethyl-3-methylbenzamide), permethrin, and mild stress by profiling the hippocampal expression of genes known to play a critical role in synaptic plasticity, glucocorticoid signaling, and neurogenesis. We determined that intracerebroventricular infusion of a miR-124 antisense oligonucleotide (miR-124 inhibitor; 0.05-0.5 nmol/day/28 days), but not a negative control oligonucleotide, into the lateral ventricle of the brain caused increased protein expression of multiple validated miR-124 targets and increased expression of downstream target genes important for cognition and neuroendocrine signaling in the hippocampus. Off-target cardiotoxic effects were revealed in GWI rats receiving 0.1 nmol/day as indicated by the detection in plasma of 5 highly elevated protein cardiac injury markers and 6 upregulated cardiac-enriched miRNAs in plasma exosomes determined by next-generation sequencing. Results from this study suggest that in vivo inhibition of miR-124 function in the hippocampus is a promising, novel therapeutic approach to improve cognition and neuroendocrine dysfunction in GWI. Additional preclinical studies in animal models to assess feasibility and safety by developing a practical, noninvasive drug delivery system to the brain and exploring potential adverse toxicologic effects of miR-124 inhibition are warranted.

CHRONIC FATIGUE SYNDROME

Increased risk of chronic fatigue syndrome following burn injuries.

Tsai SY[1,2,3], Lin CL[4,5], Shih SC[6,7], Hsu CW[8,9], Leong KH[8,9], Kuo CF[10], Lio CF[9,11], Chen YT[8,9], Hung YJ[8,9], Shi L[12].

J Transl Med. **2018 Dec 5;**16(1):342. doi: 10.1186/s12967-018-1713-2. PMID: 30518392.

BACKGROUND: The overlapping symptoms and pathophysiological similarities between burn injury and chronic fatigue syndrome (CFS) are noteworthy. Thus, this study explores the possible association between burn injury and the subsequent risk of CFS.

METHOD: We used data from the Taiwan National Health Insurance system to address the research topic. The exposure cohort comprised of 17,204 patients with new diagnoses of burn injury. Each patient was frequency matched according to age, sex, index year, and comorbidities with four participants from the general population who did not have a history of CFS (control cohort). Cox proportional hazards regression analysis was conducted to estimate the relationship between burn injury and the risk of subsequent CFS.

RESULT: The incidence of CFS in the exposure and control cohorts was 1.61 and 0.86 per 1000 person-years, respectively. The exposure cohort had a significantly higher overall risk of subsequent CFS than did the control cohort (adjusted hazard ratio [HR] = 1.48, 95% confidence interval [CI] = 1.41-1.56). The risk of CFS in patients with burn injury in whichever stratification (including sex, age, and comorbidity) was also higher than that of the control cohort.

CONCLUSION: The findings from this population-based retrospective cohort study suggest that thermal injury is associated with an increased risk of subsequent CFS and provided a point of view suggesting burn injuries in sun-exposed areas such as the face and limbs had greater impact on subsequent development of CFS compared with trunk areas. In addition, extensively burned areas and visible scars were predictors of greater physiological and psychosocial that are needed to follow-up in the long run.

CHRONIC FATIGUE SYNDROME (Continued)

Genome-epigenome interactions associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.

Herrera S[1,2], de Vega WC[1,2,3], Ashbrook D[1,2], Vernon SD[4], McGowan PO[1,2,3,5,6].

Epigenetics. **2018 Dec 5**:1-17. doi: 10.1080/15592294.2018.1549769. PMID: 30516085. [Epub ahead of print]

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex disease of unknown etiology. Multiple studies point to disruptions in immune functioning in ME/CFS patients as well as specific genetic polymorphisms and alterations of the DNA methylome in lymphocytes. However, potential interactions between DNA methylation and genetic background in relation to ME/CFS have not been examined. In this study we explored this association by characterizing the epigenetic (~480 thousand CpG loci) and genetic (~4.3 million SNPs) variation between cohorts of ME/CFS patients and healthy controls. We found significant associations of DNA methylation states in T-lymphocytes at several CpG loci and regions with ME/CFS phenotype. These methylation anomalies are in close proximity to genes involved with immune function and cellular metabolism. Finally, we found significant correlations of genotypes with methylation modifications associated with ME/CFS. The findings from this study highlight the role of epigenetic and genetic interactions in complex diseases, and suggest several genetic and epigenetic elements potentially involved in the mechanisms of disease in ME/CFS.

Rituximab Serum Concentrations and Anti-Rituximab Antibodies During B-Cell Depletion Therapy for Myalgic Encephalopathy/Chronic Fatigue Syndrome.

Rekeland IG[1], Fluge Ø[2], Alme K[2], Risa K[2], Sørland K[2], Mella O[3], de Vries A[4], Schjøtt J[5].

Clin Ther. **2018 Nov 28**. pii: S0149-2918(18)30514-9. doi: 10.1016/j.clinthera.2018.10.019. PMID: 30502905. [Epub ahead of print]

PURPOSE: Previous Phase II trials indicated clinical benefit from B-cell depletion using the monoclonal anti-CD20 antibody rituximab in patients with myalgic encephalopathy/chronic fatigue syndrome (ME/CFS). The association between rituximab serum concentrations and the effect and clinical relevance of antidrug antibodies (ADAs) against rituximab in ME/CFS is unknown. We retrospectively measured rituximab concentrations and ADAs in serum samples from patients included in an open-label Phase II trial with maintenance rituximab treatment (KTS-2-2010) to investigate possible associations with clinical improvement and clinical and biochemical data.

METHODS: Patients with ME/CFS fulfilling the Canadian criteria received rituximab (500 mg/m^2) infusions: 2 infusions 2 weeks apart (induction), followed by maintenance treatment at 3, 6, 10, and 15 months. The measured rituximab concentrations and ADAs in serum samples included 23 of 28 patients from the trial.

FINDINGS: There were no significant differences in mean serum rituximab concentrations between 14 patients experiencing clinical improvement versus 9 patients with no improvement. Female patients had higher mean serum rituximab concentrations than male patients at 3 months (P = 0.05). There was a significant negative correlation between B-cell numbers in peripheral blood at baseline and rituximab serum concentration at 3 months (r = -0.47; P = 0.03). None of the patients had ADAs at any time point.

IMPLICATIONS: Clinical improvement of patients with ME/CFS in the KTS-2-2010 trial was not related to rituximab serum concentrations or ADAs. This finding is also in line with a recent randomized trial questioning the efficacy of rituximab in ME/CFS. Rituximab concentrations and ADAs still offer supplemental information when interpreting the results of these trials.

HEADACHE and MIGRAINE

Migraine and Markers of Carotid Atherosclerosis in Middle-Aged Women: A Cross-Sectional Study.

Magalhães JE[1,2], Barros IML[3], Pedrosa RP[4], Sampaio Rocha-Filho PA [1,5,2].

Headache. **2018 Dec 5.** doi: 10.1111/head.13460. PMID: 30516278. [Epub ahead of print]

OBJECTIVE: This study evaluated the association between migraine and the markers of carotid artery disease.

BACKGROUND: Migraine increases the risk of cardiovascular events, but its relationship with vascular dysfunction is unclear.

METHODS: In this cross-sectional study, middle-aged women with no known cardiovascular diseases underwent clinical, neurological, and laboratory evaluations; pulse wave velocity (PWV) assessment; and carotid artery ultrasonography. We divided the participants based on the presence of migraine and, further, based on the type of migraine. Associations between migraine and carotid thickening (intima-media thickness >0.9 mm), carotid plaques, or arterial stiffening (PWV >10 m/s) were evaluated using a multiple regression analysis.

RESULTS: The study comprised 112/277 (40%) women with migraine, of whom 46/277 (17%) reported having an aura. Compared to the non-migraineurs, the migraine with aura group had an increased risk of diffuse carotid thickening (3/46 [6.8%] vs 2/165 [1.3%], adjusted OR = 7.12, 95% CI 1.05-48.49). Migraine without aura was associated with a low risk of carotid plaques (3/66 [4.7%] vs 26/165 [16.7%], adjusted OR = 0.28, 95% CI 0.08-0.99) and arterial stiffening (21/66 [34.4%] vs 82/165 [51.2%], adjusted OR = 0.39, 95% CI 0.19-0.79). There were no correlations between migraine characteristics and arterial stiffness or carotid thickness measurements.

CONCLUSION: Migraine with aura is associated with an increased risk of carotid thickening, and migraine without aura is associated with a low risk of carotid plaques and arterial stiffening.

Use of traditional medicine for primary headache disorders in Kuwait.

Al-Hashel JY[1,2], Ahmed SF[3,4], Alshawaf FJ[5], Alroughani R[6].

J Headache Pain. **2018 Dec 4**;19(1):118. doi: 10.1186/s10194-018-0950-3. PMID: 30514208.

BACKGROUND: Traditional Medicine (TM) is widely accepted to be used for the treatment headache disorders in Kuwait however, researches remain poorly documented. We aimed to study the frequency of TM use and its impact in the primary headache patients.

METHODS: This is a cross sectional self-reported efficacy study, which was conducted in Headache clinic in Kuwait throughout 6 months. Patients who were diagnosed with primary headache disorders of both genders aged from 18 to 65 years were included. Self-reported questionnaires were distributed to patients who used TM in the previous year. It included demographic, and characteristics of headache (headache frequency, duration, number of analgesic used in days per month and severity of headache). TM queried included blood cupping (Hijama), head banding, herbal medicine (sabkha), and diet modification. It assessed characters of headache before and 3 months after the final TM session. Independent sample t test, paired sample t test and Chi-square test were used to compare between different values. $P < 0.05$ is considered significant.

RESULTS: A total of 279 patients were included. The mean age is 40.32 ± 11.75 years; females represented 79.6% of the cohort. Most patients (n = 195; 69.9%) reported the use of TM before presentation to headache clinic, mainly Hijama (47.3%). Cultural / religious beliefs were the cause of seeking TM in 51.3% versus 10% used it due to ineffective medical treatment and 8.6% used it because of intolerance of medical treatment. Patients used TM were older at the onset of headache (24.24 ± 10.67 versus 20.38 ± 8.47; $p < 0.003$), and had longer headache disease duration (19.26 ± 13.13 versus 16.12 ± 11.39; $p < 0.044$). All patients with chronic headache (100%) and most of episodic migraine patients (90.4%) sought TM while only (31.5%) of Tension type headache sought TM; $p < 0.047$. Patients who sought TM had more frequent episodes of headache, longer duration of attacks and higher number of days of analgesic-usage respectively over last 3 months before presentation to our side (9.66 ± 7.39 versus 4.14 ± 2.72; $p < 0.001$), (41.23 ± 27.76 versus 32.19 ± 23.29; $p <. 0009$), (8.23 + 7.70 versus 3.18 ± 3.06; $p < 0.001$). At 3 months after the final TM session, there was no significant reduction of frequency of headache days per month (9.19 ± 7.33 versus 8.99 ± 7.59; $p < 0.50$), days of analgesic use per month (7.45 ± 7.43 versus 6.77 ± 6.93; $p < 0.09$) and duration of headache (41.23 ± 27.76 versus 41.59 ± 27.69; $p < 0.78$). However, there was a significant reduction of the severity of headache ($p < 0.02$). Few patients (17.9%) reported adverse events with TM. Most of TM cohorts were not satisfied after receiving this type of medicine.

CONCLUSION: TM was widely used in Kuwait for primary headache. Patients sought TM before seeking physician because they found them more congruent with their own cultural and religious beliefs. Health care professionals involved in the management of headache should be aware of this and monitor potential benefits or adverse events of TM. The usage of TM was not effective in reducing headache attacks and severity.

HEADACHE and MIGRAINE (Continued)

Investigation of association between CD40 current gene variants (rs4810485, rs1883832 and rs3765459) and serum CD154 protein levels in Iranian migraineurs.

Ramroodi N[1], Saboori H[2], Sanadgol N[3].

Cell Mol Biol (Noisy-le-grand). **2018 Nov 30**;64(14):72-78. PMID: 30511624.

Migraine is a chronic neurological disease described by recurrent moderate to severe headaches often in association with neuro-inflammation. As cytokines are affect the immune response and migraine exacerbation, the current study aimed to investigate the possible associations between CD40 polymorphisms and level of soluble CD154 protein with migraine. In a prospective case-control study, we studied blood samples of 190 patients with migraine (migraineurs) and 200 healthy controls (HCs) from southeast Iran. Genotyping for the CD40 (rs4810485-intron, rs1883832-5´-UTR, and rs3765459-intron) gene variants were executed using PCR-RFLP and soluble CD154 protein levels were measured via ELISA method. Among CD40 gene variants, rs1883832 (TC genotype) was significantly associated with migraine (P = 0.007, OR = 2.326, 95% CI = 1.258-4.303). No significant associations observed between the rs4810485 and rs3765459 SNPs with migraine. The most frequent genotypes for CD40 were GG in rs4810485 (51.5%) and rs3765459 (62.1%) as well as TC in rs1883832 (53.7%). There was no statistically relationship between these gene variants and different subclasses of migraine. Concentration of soluble CD40L among patients with rs1883832 (TC genotype) were significantly (P = 0.027, OR = 0.417, CI = 0.192-0.906) higher in compared to healthy controls. Our findings showed that in CD40 rs1883832, TC genotype may have a role in migraine susceptibility. Therefore, it suggested that in addition to other factors, CD40 rs1883832 (TC genotype) genetic variation may also play a critical role in the etiology of migraine.

Headache in the course of multiple sclerosis: a prospective study.

Gebhardt M[1], Kropp P[2], Hoffmann F[3], Zettl UK[4].

J Neural Transm (Vienna). **2018 Nov 30**. doi: 10.1007/s00702-018-1959-0. PMID: 30506270. [Epub ahead of print]

Multiple sclerosis (MS) is the most common immune-mediated inflammatory disease of the central nervous system (CNS). Early diagnosis and treatment is important to prevent progression of disability in the course of the chronic disease. Therefore, correct and fast identification of early symptoms is vital. Headache is generally not recognized as an early symptom of MS, although numerous studies could show a high prevalence of headache in MS patients. The most common misdiagnosis is migraine. The aim of this study is to investigate the prevalence as well as the phenomenology of headache in MS especially with regard to the progression of the disease. In a prospective, multicenter study, we unbiasedly recruited 150 patients with manifest MS based on the criteria of McDonald. 50 patients at the timepoint of initial diagnosis and 100 of them with a long-term course of the disease were included. Based on a semi-structured interview, we evaluated the occurrence of headache over the last 4 weeks as well as case history, clinical-neurological investigation and questionnaires about depression, fatigue, and quality of life. Prevalence of headache in all patients was 67%. Patients at the timepoint of symptom manifestation of MS showed the highest prevalence of headache that was ever been recorded of 78%. In general, patients with headache were younger, had a shorter duration of the disease, and were less physically affected. We noticed frequent occurrence of migraine and migraine-like headache. In the course of the disease, patients without disease-modifying drug (DMD) complained more frequently headaches than patients with any kind of therapy. Headache is an important early symptom of MS. This could be shown especially among 78% of patients with clinically isolated syndrome (CIS). Therefore, young people with frequent headache should undergo MRI of the head and in the case of abnormal findings a consecutive detailed differential diagnosis. This could reduce the latency until final diagnosis of MS, which is in general much too long. That way these patients could get the earliest possible treatment, which is important to stop the progression of the disease.

CHRONIC PAIN

Association between serum 25-hydroxyvitamin D levels and self-reported chronic pain in older adults: a cross-sectional analysis from the ViDA study.

Wu Z[1], Camargo CA Jr[2], Sluyter JD[1], Khaw KT[3], Malihi Z[1], Waayer D[1], Toop L[4], Lawes CMM[1], Scragg R[5].

J Steroid Biochem Mol Biol. **2018 Nov 30**. pii: S0960-0760(18)30510-7. doi: 10.1016/j.jsbmb.2018.11.018. PMID: 30508645. [Epub ahead of print]

Chronic pain is a major contributor to the global burden of disability. Prior studies on the association between serum 25-hydroxyvitamin D (25(OH)D) levels and chronic pain have yielded mixed results. The Vitamin D Assessment study, a large randomized controlled trial from New Zealand, offered the opportunity to examine this association in data collected at baseline in all participants, and among those with arthritis or depression. A total of 5110 participants aged 50-84 years were recruited from community general practices. Chronic pain (lasting ≥6 months) and other baseline characteristics were collected at baseline interview. Serum 25(OH)D concentration was measured by liquid chromatography-tandem mass spectrometry. Associations between 25(OH)D levels and chronic pain were explored using multivariable log-binomial regression to estimate relative risks (RRs). Out of 5,049 participants with complete data, 871 (17%) reported having this clinical outcome, and 1254 (25%) had a 25(OH)D concentration <50 nmol/L. There was no significant association between 25(OH)D and chronic pain, with vitamin D status categorized in four groups: <25.0, 25.0-49.9, 50.0-74.9, and ≥75.0 nmol/L (the highest group as reference). The unadjusted RRs were 1.09, 1.10, and 1.08, respectively (P_{trend} = 0.24). Adjustment for demographics, lifestyle, BMI, medical history, prescription of analgesics and vitamin D supplements did not change this finding. Similar non-significant results were observed in participants with arthritis (n = 1732) or depression (n = 528). In this multi-ethnic, community-selected sample of older adults in New Zealand, serum 25(OH)D levels were not associated with chronic pain. These results do not support a role for low vitamin D status in the prevalence of chronic pain in older adults.

Obesity increases the risk of chronic pain development following motor vehicle collision.

Mauck MC[1], Hu J[1], Sefton C[1], Swor RA[2], Peak DA[3], Jones JS[4], Rathlev NK[5], Lee DC[6], Domeier RM[7], Hendry PL[8], McLean SA[1].

Pain. **2018 Nov 29**. doi: 10.1097/j.pain.0000000000001446. PMID: 30507783. [Epub ahead of print]

Obesity has been found to increase the risk of musculoskeletal pain (MSP) in other settings, but to our knowledge the influence of increased body mass index on pain outcomes after common trauma exposures such as motor vehicle collision (MVC) has not been assessed. In addition, obesity results in biomechanical changes, as well as physiologic changes including reduced hypothalamic pituitary adrenal (HPA) axis negative feedback inhibition, but mechanisms by which obesity may result in worse post-traumatic outcomes remain poorly understood. In this study, we evaluated the influence of body mass index (BMI) on axial and overall MSP severity (0-10 numeric rating scale) 6 weeks, 6 months and 1 year after MVC among 917 European Americans who presented to the emergency department for initial evaluation. After adjusting for an array of sociodemographic factors, obesity (particularly morbid obesity) was an independent risk factor for worse MSP after MVC (e.g., RR 1.41 (95% CI 1.11, 1.80) for moderate or severe MSP 6 months after MVC among morbidly obese vs. normal weight MVC survivors). Interestingly, substantial effect modification was observed between obesity risk and a genetic variant known to reduce HPA axis negative feedback inhibition (FKBP5 rs9380526). (E.g., 41% vs. 16% increased risk of moderate or severe MSP at six months among obese individuals with and without the risk allele.) Further studies are needed to elucidate mechanisms underlying chronic pain development in obese trauma survivors and to develop interventions that will reduce chronic pain severity among this common, at risk group.

CHRONIC PAIN (Continued)

Efficacy of Low-Dose Amitriptyline for Chronic Low Back Pain: A Randomized Clinical Trial.

Urquhart DM[1], Wluka AE[1], van Tulder M[2], Heritier S[1], Forbes A[1], Fong C[3], Wang Y[1], Sim MR[1], Gibson SJ[4,5], Arnold C[6,7], Cicuttini FM[1].

JAMA Intern Med. **2018 Nov 1**;178(11):1474-1481. doi: 10.1001/jamainternmed.2018.4222. PMID: 30285054.

Importance: Antidepressants at low dose are commonly prescribed for the management of chronic low back pain and their use is recommended in international clinical guidelines. However, there is no evidence for their efficacy.

Objective: To examine the efficacy of a low-dose antidepressant compared with an active comparator in reducing pain, disability, and work absence and hindrance in individuals with chronic low back pain.

Design, Setting, and Participants: A double-blind, randomized clinical trial with a 6-month follow-up of adults with chronic, nonspecific, low back pain who were recruited through hospital/medical clinics and advertising was carried out.

Intervention: Low-dose amitriptyline (25 mg/d) or an active comparator (benztropine mesylate, 1 mg/d) for 6 months.

Main Outcomes and Measures: The primary outcome was pain intensity measured at 3 and 6 months using the visual analog scale and Descriptor Differential Scale. Secondary outcomes included disability assessed using the Roland Morris Disability Questionnaire and work absence and hindrance assessed using the Short Form Health and Labour Questionnaire.

Results: Of the 146 randomized participants (90 [61.6%] male; mean [SD] age, 54.8 [13.7] years), 118 (81%) completed 6-month follow-up. Treatment with low-dose amitriptyline did not result in greater pain reduction than the comparator at 6 (adjusted difference, -7.81; 95% CI, -15.7 to 0.10) or 3 months (adjusted difference, -1.05; 95% CI, -7.87 to 5.78), independent of baseline pain. There was no statistically significant difference in disability between the groups at 6 months (adjusted difference, -0.98; 95% CI, -2.42 to 0.46); however, there was a statistically significant improvement in disability for the low-dose amitriptyline group at 3 months (adjusted difference, -1.62; 95% CI, -2.88 to -0.36). There were no differences between the groups in work outcomes at 6 months (adjusted difference, absence: 1.51; 95% CI, 0.43-5.38; hindrance: 0.53; 95% CI, 0.19-1.51), or 3 months (adjusted difference, absence: 0.86; 95% CI, 0.32-2.31; hindrance: 0.78; 95% CI, 0.29-2.08), or in the number of participants who withdrew owing to adverse events (9 [12%] in each group; $\chi 2 = 0.004$; $P = .95$).

Conclusions and Relevance: This trial suggests that amitriptyline may be an effective treatment for chronic low back pain. There were no significant improvements in outcomes at 6 months, but there was a reduction in disability at 3 months, an improvement in pain intensity that was nonsignificant at 6 months, and minimal adverse events reported with a low-dose, modest sample size and active comparator. Although large-scale clinical trials that include dose escalation are needed, it may be worth considering low-dose amitriptyline if the only alternative is an opioid.

Trial Registration: anzctr.org.au Identifier: ACTRN12612000131853.

OTHER RESEARCH OF INTEREST

Impact of occupational exposure on human microbiota.

Lai PS[1,2,3], Christiani DC[1,2,3].

Curr Opin Allergy Clin Immunol. **2018 Nov 29**. doi: 10.1097/ACI.0000000000000502. PMID: 30507717. [Epub ahead of print]

PURPOSE OF REVIEW: Recent evidence suggests that environmental exposures change the adult human microbiome. Here, we review recent evidence on the impact of the work microbiome and work-related chemical, metal and particulate exposures on the human microbiome.

RECENT FINDINGS: Prior literature on occupational microbial exposures has focused mainly on the respiratory effects of endotoxin, but a recent study suggests that not all endotoxin is the same; endotoxin from some species is proinflammatory, whereas endotoxin from other species is anti-inflammatory. Work with animals can change the adult human microbiome, likely through colonization. Early studies in military personnel and animal models of gulf war illness show that military exposures change the gut microbiome and increase gut permeability. Heavy metal and particulate matter exposure, which are often elevated in occupational settings, also change the gut microbiome.

SUMMARY: An emerging body of literature shows that work-related exposures can change the human microbiome. The health effects of these changes are currently not well studied. If work exposures lead to disease through alterations in the human microbiome, exposure cessation without addressing changes to the human microbiome may be ineffective for disease prevention and treatment.

OTHER RESEARCH OF INTEREST (Continued)

Veterans Health Administration Hospitals Outperform Non-Veterans Health Administration Hospitals in Most Health Care Markets.

Weeks WB[1], West AN[2].

Ann Intern Med. **2018 Dec 11**. doi: 10.7326/M18-1540. PMID: 30535282. [Epub ahead of print]

See full text in Annals of Internal Medicine.

Recent studies have reported that health care provided by the Veterans Health Administration (VHA) is at least as good as that provided in the private sector. These studies tended to compare a representative sample of VHA patients or hospitals with a representative sample not in the VHA system, after adjusting for known differences that might cause misleading results. Several circumstances could explain these findings. The VHA may provide better care than the private sector in every local area. Alternatively, non-VHA care may be better than VHA care in more local areas but by a small amount, whereas VHA care may be better than non-VHA care in fewer local areas but by a large amount in each area. The average across all patients and hospitals would favor the VHA in the former circumstance and might favor the VHA in the latter. The possibility of different explanations matters, because these explanations have different implications for veterans seeking health care. For these veterans, comparisons that provide a national average may be less useful than a local comparison. For example, individual veterans probably don't care whether VHA or non-VHA hospitals provide better care on average but whether the nearest VHA hospital or the local non-VHA hospital is better for them.

Daily Drinking Is Associated with Increased Mortality.

Hartz SM[1,2], Oehlert M[2,3], Horton AC[1,2], Grucza RA[1], Fisher SL[1], Culverhouse RC[4], Nelson KG[5], Sumerall SW[2], Neal PC[2], Regnier P[2], Chen G[3], Williams A[3], Bhattarai J[2,3], Evanoff B[4], Bierut LJ[1].

Alcohol Clin Exp Res. **2018 Nov**;42(11):2246-2255. doi: 10.1111/acer.13886. PMCID: PMC6214719. PMID: 30281161. Epub 2018 Oct 3.

BACKGROUND: There is evidence that low-level alcohol use, drinking 1 to 2 drinks on occasion, is protective for cardiovascular disease, but increases the risk of cancer. Synthesizing the overall impact of low-level alcohol use on health is therefore complex. The objective of this paper was to examine the association between frequency of low-level drinking and mortality.

METHODS: Two data sets with self-reported alcohol use and mortality follow-up were analyzed: 340,668 individuals from the National Health Interview Survey (NHIS) and 93,653 individuals from the Veterans Health Administration (VA) outpatient medical records. Survival analyses were conducted to evaluate the association between low-level drinking frequency and mortality.

RESULTS: The minimum risk drinking frequency among those who drink 1 to 2 drinks per occasion was found to be 3.2 times weekly in the NHIS data, based on a continuous measure of drinking frequency, and 2 to 3 times weekly in the VA data. Relative to these individuals with minimum risk, individuals who drink 7 times weekly had an adjusted hazard ratio (HR) of all-cause mortality of 1.23 ($p < 0.0001$) in the NHIS data, and individuals who drink 4 to 7 times weekly in the VA data also had an adjusted HR of 1.23 ($p = 0.01$). Secondary analyses in the NHIS data showed that the minimum risk was drinking 4 times weekly for cardiovascular mortality, and drinking monthly or less for cancer mortality. The associations were consistent in stratified analyses of men, women, and never smokers.

CONCLUSIONS: The minimum risk of low-level drinking frequency for all-cause mortality appears to be approximately 3 occasions weekly. The robustness of this finding is highlighted in 2 distinctly different data sets: a large epidemiological data set and a data set of veterans sampled from an outpatient clinic. Daily drinking, even at low levels, is detrimental to one's health.

OTHER RESEARCH OF INTEREST (Continued)

Connection, meaning, and distraction: A qualitative study of video game play and mental health recovery in veterans treated for mental and/or behavioral health problems.

Colder Carras M[1], Kalbarczyk A[2], Wells K[3], Banks J[4], Kowert R[5], Gillespie C[6], Latkin C[7].

Soc Sci Med. **2018 Nov**;216:124-132. doi: 10.1016/j.socscimed.2018.08.044. PMCID: PMC6193255. PMID: 30257787. Epub 2018 Sep 24.

RATIONALE: Mental and behavioral health recovery includes concepts related not just to symptom improvement, but also to participating in activities that contribute to wellness and a meaningful life. Video game play can relieve stress and provide a way to connect, which may be especially important for military veterans.

OBJECTIVE: We examined how military veterans used video game play to further their mental and behavioral health recovery by conducting an exploratory thematic analysis of the gaming habits of 20 United States military veterans who were in treatment for mental or behavioral health problems.

METHOD: We conducted semi-structured interviews in 2016 and used a framework analytic approach to determine salient themes linking video gaming to mental and behavioral health recovery.

RESULTS: Veteran participants reported that video games helped not only with managing moods and stress, but also with three areas related to other aspects of recovery: adaptive coping (e.g. distraction, control, symptom substitution); eudaimonic well-being (confidence, insight, role functioning); and socializing (participation, support, brotherhood). Meaning derived from game narratives and characters, exciting or calming gameplay, and opportunities to connect, talk, and lead others were credited as benefits of gaming. Responses often related closely to military or veteran experiences. At times, excessive use of games led to life problems or feeling addicted, but some veterans with disabilities felt the advantages of extreme play outweighed these problems.

CONCLUSION: Video games seem to provide some veterans with a potent form of "personal medicine" that can promote recovery. Although reasons and results of gaming may vary within and among individuals, clinicians may wish to discuss video game play with their patients to help patients optimize their use of games to support recovery.

Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men: A Systematic Review and Meta-analysis.

Walther A[1,2,3], Breidenstein J[1], Miller R[1,4].

JAMA Psychiatry. **2018 Nov 14**. doi: 10.1001/jamapsychiatry.2018.2734. PMID: 30427999. [Epub ahead of print]

Importance: Countering depressive disorders is a public health priority. Currently, antidepressants are the first-line treatment, although they show modest effects. In men, testosterone treatment is a controversial alternative or adjunct treatment option.

Objectives: To examine the association of testosterone treatment with alleviation of depressive symptoms in men and to clarify moderating effects of testosterone status, depression status, age, treatment duration, and dosage.

Data Sources: English-language studies published in peer-reviewed journals identified from PubMed/Medline, Embase, Scopus, PsychINFO, and the Cochrane Controlled Trials Register from database inception to March 5, 2018, using the search terms testosterone, mood, administration, dosage, adverse effects, deficiency, standards, therapeutic use, therapy, treatment, and supplementation.

Study Selection: Randomized placebo-controlled clinical trials (RCTs) of testosterone treatment that together cover a broad age range and hypogonadal or eugonadal men reporting depressive symptoms on psychometrically validated depression scales.

Data Extraction and Synthesis: Of 7690 identified records, 469 were evaluated against full study inclusion criteria after removing duplicates, reviews, and studies that did not examine male patients or testosterone. Quality assessment and data extraction from the remaining 27 RCTs were performed.

Main Outcomes and Measures: Primary outcomes were testosterone treatment effectiveness (standardized score difference after treatment), efficacy (proportion of patients who responded to testosterone treatment with a score reduction of 50% or greater), and acceptability (proportion of patients who withdrew for any reason).

Results: Random-effects meta-analysis of 27 RCTs including 1890 men suggested that testosterone treatment is associated with a significant reduction in depressive symptoms compared with placebo (Hedges g, 0.21; 95% CI, 0.10-0.32), showing an efficacy of odds ratio (OR), 2.30 (95% CI, 1.30-4.06). There was no significant difference between acceptability of testosterone treatment and placebo (OR, 0.79; 95% CI, 0.61-1.01). Meta-regression models suggested significant interactions for testosterone treatment with dosage and symptom variability at baseline. In the most conservative bias scenario, testosterone treatment remained significant whenever dosages greater than 0.5 g/wk were administered and symptom variability was kept low.

Conclusions and Relevance: Testosterone treatment appears to be effective and efficacious in reducing depressive symptoms in men, particularly when higher-dosage regimens were applied in carefully selected samples. However, given the heterogeneity of the included RCTs, more preregistered trials are needed that explicitly examine depression as the primary end point and consider relevant moderators.

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