GULF WAR ILLNESS

Gulf war illness-related chemicals increase CD11b/c+ monocyte infiltration into the liver and aggravate hepatic cholestasis in a rodent model.
Petrescu AD1,2, Grant S1,2, Frampton G1,2, McMillin M2, Kain J1, Kodali M2,3, Shetty AK2,3, DeMorrow S4,5.

Gulf War Illness (GWI) is a chronic multisymptom disorder affecting veterans of the 1990-91 Gulf war. GWI was linked with exposure to chemicals including the nerve gas prophylactic drug pyridostigmine-bromide (PB) and pesticides (DEET, permethrin). Veterans with GWI exhibit prolonged, low-level systemic inflammation, though whether this impacts the liver is unknown. While no evidence exists that GWI-related chemicals are hepatotoxic, the prolonged inflammation may alter the liver's response to insults such as cholestatic injury. We assessed the effects of GWI-related chemicals on macrophage infiltration and its subsequent influence on hepatic cholestasis. Sprague Dawley rats were treated daily with PB, DEET and permethrin followed by 15 minutes of restraint stress for 28 days. Ten weeks afterward, GWI rats or naïve age-matched controls underwent bile duct ligation (BDL) or sham surgeries. Exposure to GWI-related chemicals alone increased IL-6, and CD11b+F4/80- macrophages in the liver, with no effect on biliary mass or hepatic fibrosis. However, pre-exposure to GWI-related chemicals enhanced biliary hyperplasia and fibrogenesis caused by BDL, compared to naïve rats undergoing the same surgery. These data suggest that GWI patients could be predisposed to developing worse liver pathology due to sustained low-level inflammation of the liver when compared to patients without GWI.

CHRONIC FATIGUE SYNDROME

Prevalence and incidence of myalgic encephalomyelitis/chronic fatigue syndrome in Europe—the Euro-epiME study from the European network EUROMENE: a protocol for a systematic review.
Estévez-López F1,2,3, Castro-Marrero J4,5, Wang X6, Bakken IJ7, Ivanovs A8, Nacul L9, Sepúlveda N10, Strand EB11, Pheby D12, Alegre J4, Scheibenbogen C13, Shikova E14, Lorusso L15, Capelli E16, Sekulic S17, Lacerda E18, Murovska M19; European Network on ME/CFS (EUROMENE).

INTRODUCTION: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease involving central nervous system and immune system disorders, as well as cardiovascular abnormalities. ME/CFS is characterised by severe chronic fatigue lasting for at least 6 months, including clinical symptoms such as tender cervical or axillary lymph nodes, muscle pain, joint pain without swelling or redness, post-exertional malaise for more than 24 hours and unrefreshing sleep. Studies on the epidemiology of ME/CFS in Europe only include single countries and, therefore, the prevalence and incidence of ME/CFS in Europe (as a whole) is unknown. One of the purposes of the European Network on ME/CFS (EUROMENE; European Union-funded COST Action; Reference number: 15111) is to address this gap in knowledge. We will systematically review the literature reporting figures from European countries to provide a robust summary and identify new challenges.

METHODS AND ANALYSIS: We will systematically search the literature databases Scopus, PubMed and Web of Science for studies published in the last 10 years (ie, after 2007). No language restriction will be applied. Two independent reviewers will search, screen and select studies as well as extract data about their main characteristics and evaluate their methodological and reporting quality. When disagreements emerge, the reviewers will discuss to reach a consensus. We plan to produce a narrative summary of our findings as we anticipate that studies are scarce and heterogeneous. The possibility of performing meta-analyses will be discussed in a EUROMENE meeting.

ETHICS AND DISSEMINATION: Ethical approval is not required as only publicly available data will be included. Findings will be described in EUROMENE reports, published in peer-reviewed journal(s) and presented at conferences. The findings will be also communicated to policy-makers, healthcare providers, people with ME/CFS and other sections of society through regular channels including the mass-media.

PROSPERO REGISTRATION NUMBER: CRD42017078688.
**CHRONIC FATIGUE SYNDROME (Continued)**

**Confirmatory factor analysis of a myalgic encephalomyelitis and chronic fatigue syndrome stigma scale.**

Terman JM¹, Awsumb JM¹, Cotler J¹, Jason LA¹.

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This study adapted a chronic illness stigma scale and explored its psychometric properties. The main purposes were to confirm the factor structure of the instrument with this population and address the previous factor intercorrelation discrepancies. Five hundred and forty-five individuals with myalgic encephalomyelitis or chronic fatigue syndrome completed the adapted stigma scale. Results document the stigma experienced by an international sample of individuals with myalgic encephalomyelitis and chronic fatigue syndrome. Factors demonstrated good internal consistency, and a model fit was found in a confirmatory factor analysis. Participants endorsed high levels of stigma, estrangement, and disclosure. Implications of these findings and future directions are discussed.

**HEADACHE and MIGRAINE**

**Direct and Indirect Costs Among United States Commercially Insured Employees With Migraine.**

Gilligan AM¹, Foster SA, Sainski-Nguyen A, Sedgley R, Smith D, Morrow P.


OBJECTIVE: To compare direct, indirect, and societal (direct plus indirect) costs between patients with and without migraine (controls).

METHODS: Patients with migraine were identified from MarketScan claims and Health and Productivity Management databases from 01/01/2010-12/31/2013, and were propensity score matched (1:1) to controls.

RESULTS: Patients with migraine (N=26,647) were matched to controls, of which 4,323 were matched for work absence and 26,212 for short-term disability eligibility. Mean annualized direct costs ($13,032 vs $3,234), indirect costs due to absence ($4,104 vs $3,531) and short-term disability ($1,131 vs $52), and societal costs due to absence ($16,043 vs $6,938) and short-term disability ($14,278 vs $3,182) were all significantly higher (P<0.001) for those patients with migraine versus controls, respectively.

CONCLUSIONS: Migraine imposes high direct and indirect economic burden on payers and society due to significantly higher work productivity loss compared to controls.

**Headache Attributed to TMD Is Associated With the Presence of Comorbid Bodily Pain: A Case-Control Study.**

Vivaldi D¹, Di Giosia M², Tchivileva IE², Jay GW³, Slade GD⁴, Lim PF².


Headache attributed to temporomandibular disorders (TMDH) is defined as a secondary headache by the International Classification of Headache Disorders 3rd edition (ICHD-3).

OBJECTIVE: The objective of this case-control study is to investigate the phenotypic characteristics of chronic TMD with and without TMDH. We hypothesize that chronic TMD with TMDH is associated with increased number of bodily pain conditions, more painful sites in the head and neck region, and greater TMD pain intensity.

METHODS: This is a retrospective cross-sectional review of the medical records of consecutive patients who sought treatment at the University of North Carolina Orofacial Pain Clinic between 2013 and 2014. The inclusion criterion was a diagnosis of myalgia or arthralgia according to the Research Diagnostic Criteria for Temporomandibular Disorders. In addition, cases had a diagnosis of TMDH according to the ICHD-3 criteria. Data on the presence and the number of self-reported bodily pain conditions (such as fibromyalgia and low back pain), pain intensity, number of painful sites in the head and neck upon palpation, and TMD pain onset were analyzed.

RESULTS: A total of 295 records were reviewed. Thirty-four (29.3%) patients fulfilled inclusion criteria for cases (TMD+TMDH) and 82 (70.7%) for controls (TMD-TMDH). Cases reported greater number of bodily pain conditions than controls, with a mean of 1.97 ± 1.50 and 1.26 ± 1.28 of bodily pain conditions, respectively (P = .012, OR = 1.43 [95% CI 1.07-1.92]). In fact, 55.9% of cases reported at least 2 comorbid pain conditions compared to 37.8% controls (P = .044). Compared to controls (8.65 ± 5.32), cases (13.05 ± 4.46) exhibited greater number of painful sites upon palpation in the head and neck region (P < .0001, OR = 1.18 [95% CI 1.09-1.30]), and greater TMD pain intensity, with a mean of 6.00 ± 2.17 for cases and 5.09 ± 2.14 for controls (P = .041, OR = 1.22 [95% CI 1.01-1.47]).

CONCLUSION: In a population of patients with chronic TMD seeking pain management, TMDH was significantly associated with an increased number of self-reported bodily pain conditions, a greater number of painful sites in the head and neck regions, and higher TMD pain intensity.
Impact of cluster headache on employment status and job burden: a prospective cross-sectional multicenter study.


BACKGROUND: Cluster headaches (CH) are recurrent severe headaches, which impose a major burden on the life of patients. We investigated the impact of CH on employment status and job burden.

METHODS: The study was a sub-study of the Korean Cluster Headache Registry. Patients with CH were enrolled from September 2016 to February 2018 from 15 headache clinics in Korea. We also enrolled a headache control group with age-sex matched patients with migraine or tension-type headache. Moreover, a control group including individuals without headache complaints was recruited. All participants responded to a questionnaire that included questions on employment status, type of occupation, working time, sick leave, reductions in productivity, and satisfaction with current occupation. The questionnaire was administered to participants who were currently employed or had previous occupational experience.

RESULTS: We recruited 143 patients with CH, 38 patients with other types of headache (migraine or tension-type headache), and 52 headache-free controls. The proportion of employees was lower in the CH group compared with the headache and headache-free control groups (CH: 67.6% vs. headache controls: 84.2% vs. headache-free controls: 96.2%; p = 0.001). The CH group more frequently experienced difficulties at work and required sick leave than the other groups (CH: 84.8% vs. headache controls: 63.9% vs. headache-free controls: 36.5%; p < 0.001; CH: 39.4% vs. headache controls: 13.9% vs. headache-free controls: 3.4%; p < 0.001). Among the patients with CH, sick leave was associated with younger age at CH onset (25.8 years vs. 30.6 years, p = 0.014), severity of pain rated on a visual analogue scale (9.3 vs. 8.8, p = 0.008), and diurnal periodicity during the daytime (p = 0.003). There were no significant differences with respect to the sick leave based on sex, age, CH subtypes, and CH recurrence.

CONCLUSIONS: CH might be associated with employment status. Most patients with CH experienced substantial burdens at work.

A randomized, double-blinded, placebo-controlled, parallel trial of vitamin D₃ supplementation in adult patients with migraine.

Gazerani P1, Fuglsang R1, Pedersen JG1, Sørensen J1, Kjeldsen JL1, Yassin H1, Nedergaard BS2.


BACKGROUND: Vitamin D levels have been linked to certain pain states, including migraine. We investigated whether vitamin D supplementation would be beneficial for adult patients with migraine (ClinicalTrials.gov Identifier: NCT01695460).

METHODS: A randomized, double-blind, placebo-controlled parallel trial was conducted in migraine patients (36 women and 12 men, 18-65 years of age). A 4-week baseline period was conducted before randomization to 24 weeks of treatment. Participants were assigned to receive D₃-Vitamin® (n = 24, 18 women and 6 men, 100 μg/day D₃-Vitamin®) or placebo (n = 24, 18 women and 6 men). Migraine attacks and related symptoms were assessed by self-reported diaries. The response rate (i.e., experiencing a 50% or greater reduction in migraine frequency from baseline to week 24), change in migraine severity, and number of migraine days were recorded. Changes in migraine-related symptoms, HIT-6™ scores, and pain sensitivity tests (pressure pain threshold and temporal summation) were also evaluated. Serum levels of both 25(OH)D and 1,25(OH)₂D were assessed from baseline to week 24.

RESULTS: The number of headache days changed from 6.14±3.60 in the treatment group and 5.72±4.52 in the placebo group at baseline to 3.28±3.24 and 4.93±3.24 by the end of the trial, respectively. Migraine patients on D₃-Vitamin® demonstrated a significant decrease (p < 0.001) in migraine frequency from baseline to week 24 compared with placebo. However, migraine severity, pressure pain thresholds or temporal summation did not show a significant change. 25(OH)D levels increased significantly for the D₃-Vitamin® group during the first 12 weeks of treatment. There was no significant change in 1,25(OH)₂D. No side effects were reported or noted.

CONCLUSIONS: D₃-Vitamin® was superior to placebo in reducing migraine days in migraine patients. Larger studies are required to confirm that vitamin D₃ might be one of the prophylactic options for adult patients with migraine.
CHRONIC PAIN

Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity.
Weizman L1, Dayan L1, Brill S1, Nahman-Averbuch H1, Hendler T1, Jacob G1, Sharon H2.

OBJECTIVE: To characterize the functional brain changes involved in δ-9-tetrahydrocannabinol (THC) modulation of chronic neuropathic pain.

METHODS: Fifteen patients with chronic radicular neuropathic pain participated in a randomized, double-blind, placebo-controlled trial employing a counterbalanced, within-subjects design. Pain assessments and functional resting state brain scans were performed at baseline and after sublingual THC administration. We examined functional connectivity of the anterior cingulate cortex (ACC) and pain-related network dynamics using graph theory measures.

RESULTS: THC significantly reduced patients' pain compared to placebo. THC-induced analgesia was correlated with a reduction in functional connectivity between the anterior cingulate cortex (ACC) and the sensorimotor cortex. Moreover, the degree of reduction was predictive of the response to THC. Graph theory analyses of local measures demonstrated reduction in network connectivity in areas involved in pain processing, and specifically in the dorsolateral prefrontal cortex (DLPFC), which were correlated with individual pain reduction.

CONCLUSION: These results suggest that the ACC and DLPFC, 2 major cognitive-emotional modulation areas, and their connections to somatosensory areas, are functionally involved in the analgesic effect of THC in chronic pain. This effect may therefore be mediated through induction of functional disconnection between regulatory high-order affective regions and the sensorimotor cortex. Moreover, baseline functional connectivity between these brain areas may serve as a predictor for the extent of pain relief induced by THC.

Patterns of conventional and complementary non-pharmacological health practice use by US military veterans: a cross-sectional latent class analysis.
Donaldson MT1,2, Polusny MA3,4, MacLehose RF5, Goldsmith ES3,5, Hagel Campbell EM3, Miron LR3, Thuras PD3, Krebs EE3,4.

BACKGROUND: Non-pharmacological therapies and practices are commonly used for both health maintenance and management of chronic disease. Patterns and reasons for use of health practices may identify clinically meaningful subgroups of users. The objectives of this study were to identify classes of self-reported use of conventional and complementary non-pharmacological health-related practices using latent class analysis and estimate associations of participant characteristics with class membership.

METHODS: A mailed survey (October 2015 to September 2016) of Minnesota National Guard Veterans from a longitudinal cohort (n = 1850) assessed current pain, self-reported overall health, mental health, substance use, personality traits, and health practice use. We developed the Health Practices Inventory, a self-report instrument assessing use of 19 common conventional and complementary non-pharmacological health-related practices. Latent class analysis was used to identify subgroups of health practice users, based on responses to the HPI. Participants were assigned to their maximum-likelihood class, which was used as the outcome in multinomial logistic regression to examine associations of participant characteristics with latent class membership.

RESULTS: Half of the sample used non-pharmacological health practices. Six classes of users were identified. "Low use" (50%) had low rates of health practice use. "Exercise" (23%) had high exercise use. "Psychotherapy" (6%) had high use of psychotherapy and support groups. "Manual therapies" (12%) had high use of chiropractic, physical therapy, and massage. "Mindfulness" (5%) had high use of mindfulness and relaxation practice. "Multimodal" (4%) had high use of most practices. Use of manual therapies (chiropractic, acupuncture, physical therapy, massage) was associated with chronic pain and female sex. Characteristics that predict use patterns varied by class. Use of self-directed practices (e.g., aerobic exercise, yoga) was associated with the personality trait of absorption (openness to experience). Use of psychotherapy was associated with higher rates of psychological distress.

CONCLUSIONS: These observed patterns of use of non-pharmacological health practices show that functionally similar practices are being used together and suggest a meaningful classification of health practices based on self-directed/active and practitioner-delivered. Notably, there is considerable overlap in users of complementary and conventional practices.
CHRONIC PAIN (Continued)

**Relationship Between Opioid Analgesic Prescription and Unemployment in Patients Seeking Acupuncture for Chronic Pain in Urban Primary Care.**

Chuang E¹, Gil EN¹, Gao Q², Kligler B³, McKee MD¹.


**Objective:** The widespread use of opioid analgesics to treat chronic nonmalignant pain has contributed to the ongoing epidemic of opioid-related morbidity and mortality. Previous studies have also demonstrated a relationship between opioid analgesic use and unemployment due to disability. These studies have been limited to mainly white European and North American populations. The objective of this study is to explore the relationship between opioid analgesic use for chronic nonmalignant pain in an urban, mainly black and Hispanic, low-income population.

**Design:** This is a cross-sectional observational study.

**Setting:** Subjects were recruited from six urban primary care health centers.

**Subjects:** Adults with chronic neck, back, or osteoarthritis pain participating in an acupuncture trial were included.

**Methods:** Survey data were collected as part of the Acupuncture Approaches to Decrease Disparities in Pain Treatment two-arm (AADDOPT-2) comparative effectiveness trial. Participants completed a baseline survey including employment status, opioid analgesic use, the Brief Pain Inventory, the global Patient Reported Outcomes Measurement Information Systems quality of life measure, the Patient Health Questionnaire-9 (PHQ-9), and demographic information. A multivariable logistic regression model was built to examine the association between opioid analgesic use and unemployment.

**Results:** Opioid analgesic use was associated with three times the odds of unemployment due to disability while controlling for potential confounders, including depression, pain severity, pain interference, global physical and mental functioning, and demographic characteristics.

**Conclusions:** This study adds to the growing body of evidence that opioid analgesics should be used with caution in chronic nonmalignant pain.

**OTHER RESEARCH OF INTEREST**

**The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS): progress toward understanding suicide among soldiers.**

Naifeh JA¹, Mash HBH¹, Stein MB²,³, Fullerton CS¹, Kessler RC⁴, Ursano RJ⁵.


Responding to an unprecedented increase in the suicide rate among soldiers, in 2008 the US Army and US National Institute of Mental Health funded the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS), a multicomponent epidemiological and neurobiological study of risk and resilience factors for suicidal thoughts and behaviors, and their psychopathological correlates among Army personnel. Using a combination of administrative records, representative surveys, computerized neurocognitive tests, and blood samples, Army STARRS and its longitudinal follow-up study (STARRS-LS) are designed to identify potentially actionable findings to inform the Army's suicide prevention efforts. The current report presents a broad overview of Army STARRS and its findings to date on suicide deaths, attempts, and ideation, as well as other important outcomes that may increase suicide risk (e.g., mental disorders, sexual assault victimization). The findings highlight the complexity of environmental and genetic risk and protective factors in different settings and contexts, and the importance of life and career history in understanding suicidal thoughts and behaviors.
Risk Factors Associated With Attempted Suicide Among US Army Soldiers Without a History of Mental Health Diagnosis.

Ursano RJ1, Kessler RC2, Saief FA1, Herberman Mash HB1, Nock MK3, Aliaga PA1, Fullerton CS1, Wynn GH1, Ng THH1, Dinh HM1, Sampson NA2, Kao TC4, Heeringa SG5, Stein MB6,7,8.


Importance: The US Army suicide attempt rate increased sharply during the wars in Afghanistan and Iraq. Although soldiers with a prior mental health diagnosis (MH-Dx) are known to be at risk, little is known about risk among those with no history of diagnosis.

Objective: To examine risk factors for suicide attempt among soldiers without a previous MH-Dx.

Design, Setting, and Participants: In this retrospective longitudinal cohort study using administrative data from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS), person-month records were identified for all active-duty Regular Army enlisted soldiers who had a medically documented suicide attempt from January 1, 2004, through December 31, 2009 (n = 9650), and an equal-probability sample of control person-months (n = 153,528). Data analysis in our study was from September 16, 2017, to June 6, 2018. In a stratified sample, it was examined whether risk factors for suicide attempt varied by history of MH-Dx.

Main Outcomes and Measures: Suicide attempts were identified using Department of Defense Suicide Event Report records and International Classification of Diseases, Ninth Revision, Clinical Modification E95 < diagnostic codes. Mental health diagnoses and related codes, as well as sociodemographic, service-related, physical health care, injury, subject to crime, crime perpetration, and family violence variables, were constructed from Army personnel, medical, legal, and family services records.

Results: Among 9650 enlisted soldiers with a documented suicide attempt (74.8% male), 3507 (36.3%) did not have a previous MH-Dx. Among soldiers with no previous diagnosis, the highest adjusted odds of suicide attempt were for the following: female sex (odds ratio [OR], 2.6; 95% CI, 2.4-2.8), less than high school education (OR, 1.9; 95% CI, 1.8-2.0), first year of service (OR, 6.0; 95% CI, 4.7-7.7), previously deployed (OR, 2.4; 95% CI, 2.1-2.8), promotion delayed 2 months or less (OR, 2.1; 95% CI, 1.7-2.6), past-year demotion (OR, 1.8; 95% CI, 1.3-1.8), 8 or more outpatient physical health care visits in the past 2 months (OR, 3.3; 95% CI, 2.9-3.8), past-month injury-related outpatient (OR, 3.0; 95% CI, 2.8-3.3) and inpatient (OR, 3.8; 95% CI, 2.3-6.3) health care visits, previous combat injury (OR, 1.6; 95% CI, 1.0-2.4), subjection to minor violent crime (OR, 1.6; 95% CI, 1.1-2.4), major violent crime perpetration (OR, 2.0; 95% CI, 1.3-3.0), and family violence (OR, 2.9; 95% CI, 1.9-4.4). Most of these variables were also associated with suicide attempts among soldiers with a previous MH-Dx, although the strength of associations differed.

Conclusions and Relevance: Suicide attempt risk among soldiers with unrecognized mental health problems is a significant and important challenge. Administrative records from personnel, medical, legal, and family services systems can assist in identifying soldiers at risk.


Reger MA1,2, Smolenski D3, Carter SP1.


Editorial Commentary on above Ursano et al. Risk Factors Associated With Attempted Suicide Among US Army Soldiers…

Suicide behaviors are frequently conceptualized as a mental health problem. There is certainly a substantial body of research indicating that various mental health disorders increase the risk of suicide and suicide attempts. Further, psychological autopsies conducted on those who died by suicide reveal mental health diagnoses in about 90% of cases. However, only half of the individuals who die by suicide are diagnosed as having a mental health disorder before their death. While the importance of psychiatric disorders to suicide behaviors is clear, together, these numbers also indicate that there is a considerable number of at-risk individuals who have not been identified and thus treated for an existing mental health disorder before suicide.

In JAMA Psychiatry, Ursano et al assess administrative data from the Army Study to Assess Risk and Resilience in Servicemembers including 9650 enlisted soldiers with a medically documented suicide attempt and more than 153,000 control person-months to examine differences in those with and without a history of mental health diagnoses. Similar to prior military surveillance reports, 36.3% (3507 of 9650) of soldiers with a documented suicide attempt had not received a mental health diagnosis prior to their attempt. This finding is particularly notable given the study’s liberal definition of mental health diagnosis, which included a single diagnosis by any type of clinician, including mental health–related V-codes, such as marital problems and other stressors. Overall, these data suggest that a significant proportion of at-risk soldiers may not have benefitted from screening and intervention efforts conducted within the Army’s mental health system. [See full text of this article in JAMA Psychiatry.]
Using the Common-Sense Model to Understand Health Outcomes for Medically Unexplained Symptoms: A Meta-Analysis.

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Consistent with the common-sense model of self-regulation, illness representations are considered the key to improving health outcomes for medically unexplained symptoms and illnesses (MUS). Which illness representations are related to outcomes and how they are related is not well understood. In response, we conducted a meta-analysis of the relationship between illness representations, self-management/coping, and health outcomes (perceived disease state, psychological distress, and quality of life) for patients with MUS. We reviewed 23 studies and found that threat-related illness representations and emotional representations were related to worse health outcomes and more negative coping (moderate to large effect). Generally, increases in negative coping mediated (with a moderate to large effect) the relationship of threat/emotional illness representations and health outcomes. Protective illness representations were related to better health outcomes, less use of negative coping and greater use of positive coping (small to moderate effect). The relationship of protective illness representations to better health outcomes was mediated by decreases in negative coping (moderate to large effect) and increases in positive coping (moderate effect). Perceiving a psychological cause to the MUS was related to more negative health outcomes (moderate to large effect) and more negative emotional coping (small effect). The relationship of perceiving a psychological cause and more negative health outcomes was mediated by increases in negative emotional coping. Improving our understanding of how illness representations impact health outcomes can inform efforts to improve treatments for MUS. Our results suggest behavioural treatments should focus on reducing threat-related illness representations and negative coping.