GULF WAR ILLNESS

Adverse effects of Gulf War Illness (GWI) serum on neural cultures and their prevention by healthy serum

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Gulf War Illness (GWI) is a chronic debilitating disease of unknown etiology that affects the brain and has afflicted many veterans of the 1990-91 Gulf War (GW). Here we tested the hypothesis that brain damage may be caused by circulating harmful substances to which GW veterans were exposed but which could not be eliminated due to lack of specific immunity. We assessed the effects of serum from GWI patients on function and morphology of brain cultures in vitro, including cultures of embryonic mouse brain and neuroblastoma N2A line. Blood serum from GWI and healthy GW veterans was added, alone and in combination, to the culture and its effects on the function and morphology of the culture assessed. Neural network function was assessed using electrophysiological recordings from multielectrode arrays in mouse brain cultures, whereas morphological assessments (neural growth and cell apoptosis) were done in neuroblastoma cultures. In contrast to healthy serum, the addition of GWI serum disrupted neural network communication and caused reduced cell growth and increased apoptosis. All of these detrimental effects were prevented or ameliorated by the concomitant addition of serum from healthy GW veterans. These findings indicate that GWI serum contains neuropathogenic factors that can be neutralized by healthy serum. We hypothesize that these factors are persistent antigens circulating in GWI blood that can be neutralized, possibly by specific antibodies present in the healthy serum, as proposed earlier.

Human Immunoglobulin G (IgG) Neutralizes Adverse Effects of Gulf War Illness (GWI) Serum in Neural Cultures: Paving the Way to Immunotherapy for GWI

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Gulf War Illness (GWI) is a chronic debilitating disease of unknown etiology that affects the brain and has afflicted many veterans of the 1990-91 Gulf War (GW). We showed recently1 that blood serum from patients suffering from GWI exerts detrimental effects on neural cultures, including reduced growth, increased apoptosis, and disruption of neural network function. Remarkably, these adverse effects were prevented by the concomitant addition to the culture of serum from healthy Gulf War (GW) era veterans. We interpreted those findings1 in the context of our hypothesis that GWI is, at least partly, due to circulating pathogenic persistent antigens2, probably coming from vaccines administered to GW veterans who lacked crucial Human Leukocyte Antigen (HLA) class 2 alleles3 and, therefore, could not make antibodies against those antigens; by contrast, healthy GW veterans who received the same vaccines and possessed HLA protection3 made antibodies that neutralized the various antigens. Thus, we hypothesized that the beneficial effect of the healthy serum on preventing the adverse GWI serum effects was due to the presence of antibodies against the persistent antigens. Here we tested this hypothesis by assessing the effect of pooled human immunoglobulin G (IgG) on ameliorating the GWI adverse effects on neural growth and apoptosis in neuroblastoma N2A cultures. We tested this effect in 14 GWI patients and found that IgG exerted a potent ameliorating effect by inhibiting the reduction in growth and increased apoptosis of GWI serum. These results lend support to our persistent antigen hypothesis1,2 and suggest an immunotherapy approach for treating GWI. This approach is further strengthened by our finding that the severity of GWI neurocognitive/mood (NCM) symptoms was positively correlated with the degree of apoptosis caused by GWI serum on the neural culture, thus validating the relevance of the apoptotic effect to NCM symptomatology. Finally, we used this relation to predict NCM scores based on the reduced apoptosis effected by IgG addition and found a predicted reduction in NCM symptom severity by ~60%. Altogether, these findings point to the possible beneficial use of IgG in treating GWI.

CHRONIC FATIGUE SYNDROME

Hyperintense sensorimotor T1 spin echo MRI is associated with brainstem abnormality in chronic fatigue syndrome.

Barnden LR[1], Shan ZY[2], Staines DR[3], Marshall-Gradisnik S[4], Finegan K[5], Ireland T[6], Bhuta S[7].

We recruited 43 Chronic Fatigue Syndrome (CFS) subjects who met Fukuda criteria and 27 healthy controls and performed 3T MRI T1 and T2 weighted spin-echo (T1wSE and T2wSE) scans. T1wSE signal follows T1 relaxation rate (1/T1 relaxation time) and responds to myelin and iron (ferritin) concentrations. We performed MRI signal level group comparisons with SPM12. Spatial normalization after segmentation was performed using T2wSE scans and applied to the coregistered T1wSE scans. After global signal-level normalization of individual scans, the T1wSE group comparison detected decreased signal-levels in CFS in a brainstem region (cluster-based inference controlled for family wise error rate, $P_{FWE} = 0.002$), and increased signal-levels in large bilateral clusters in sensorimotor cortex white matter (cluster $P_{FWE} < 0.0001$). Moreover, the brainstem T1wSE values were negatively correlated with the sensorimotor values for both CFS ($R^2 = 0.31$, $P = 0.00007$) and healthy controls ($R^2 = 0.34$, $P = 0.0009$), and the regressions were co-linear. This relationship, previously unreported in either healthy controls or CFS, in view of known thalamic projection-fibre plasticity, suggests brainstem conduction deficits in CFS may stimulate the upregulation of myelin in the sensorimotor cortex to maintain brainstem - sensorimotor connectivity. VBM did not find group differences in regional grey matter or white matter volumes. We argued that increased T1wSE observed in sensorimotor WM in CFS indicates increased myelination which is a regulatory response to deficits in the brainstem although the causality cannot be tested in this study. Altered brainstem myelin may have broad consequences for cerebral function and should be a focus of future research.

HEADACHE and MIGRAINE

Retrospective review of thienopyridine therapy in migraineurs with patent foramen ovale.

Sommer RJ[1], Nazif T[2], Privitera L[2], Robbins BT[2].

OBJECTIVE: We retrospectively reviewed our clinical experience using off-label thienopyridine agents in patients with migraine headache (MHA) and patent foramen ovale (PFO).

METHODS: Between 2011 and 2017, MHA/PFO patients referred to our practice were clinically treated with clopidogrel specifically for MHA. Those with ≥50% reduction in monthly MHA days compared with baseline were deemed MHA responders. MHA nonresponders with inadequate platelet inhibition by PRU testing were offered prasugrel. Thienopyridine-responsive patients were then offered PFO closure.

RESULTS: Of 136 patients (86% female, mean age 37.9 years, mean MHA burden 14.7 days/month), 80 (59%) were MHA responders to clopidogrel. The clopidogrel responder rate was equivalent in episodic, chronic, aura, and nonaura subgroups. A total of 19/45 (40%) MHA nonresponders had inadequate platelet inhibition by PRU testing on clopidogrel. Sixteen of those patients received prasugrel, were adequately platelet inhibited by PRU, and 10/16 (62%) converted to MHA responders. A total of 56/90 thienopyridine-responsive patients underwent subsequent PFO closure with thienopyridine discontinuation after 3 months. Ninety-four percent had ongoing MHA relief. A total of 8/8 responders who stopped thienopyridine without PFO closure had resumption of MHA symptoms.

CONCLUSION: Successful P2Y12 platelet inhibition seemed to reduce MHA symptoms in some patients with PFO, suggesting a platelet-based mechanism/trigger. The nearly parallel response to PFO closure may mechanistically link venous platelet activation with the right-to-left shunt of PFO. Thienopyridine responsiveness could be used to enrich the study population for a new MHA/PFO trial.

CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that in patients with PFO, P2Y12 inhibition improved MHA symptoms.

HEADACHE and MIGRAINE (Continued)

Ticagrelor for Refractory Migraine/Patent Foramen Ovale (TRACTOR): An open-label pilot study.

Reisman AM[1], Robbins BT[1], Chou DE[1], Yugrakh MS[1], Gross GJ[1], Privitera L[1], Nazif T[1], Sommer RJ[2].

OBJECTIVE: After finding that the thienopyridines clopidogrel and prasugrel reduced migraine headache (MHA) symptoms in some patients with patent foramen ovale (PFO), this small pilot study was undertaken to determine whether ticagrelor, a nonthienopyridine P2Y12 inhibitor, would have similar MHA effects and might be better suited for a future randomized trial.

METHODS: MHA patients were screened for PFO. Participants with documented right to left shunt (RLS) and ≥6 monthly MHA days received ticagrelor therapy for 28 days. Those with ≥50% reduction in monthly MHA days were deemed responders and completed 2 additional treatment months.

RESULTS: The 40 participants had a mean age of 36.2 years and mean MHA frequency of 17.4 d/mo. A total of 39/40 were female. A total of 14/40 met criteria for episodic MHA, 26/40 for chronic MHA, 14/40 had migraine with aura, and 22/40 had a moderate-large RLS (Spencer grade ≥4). Seventeen of 40 participants (43%) were responders. MHA reduction continued through 3 treatment months in all responders. MHA responder rates were not statistically different in participants with episodic or chronic MHA, with or without aura, or with small/larger RLS shunt magnitude. Thirteen (32%) patients had medication side effects, without serious adverse events.

CONCLUSION: P2Y12 inhibition with ticagrelor reduced MHA symptoms similarly to our previous thienopyridine experience, but participants seemed to have a less robust MHA benefit and more frequent side effects than with the thienopyridines, making it an inferior choice for a randomized trial.

CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that ticagrelor reduced MHA symptoms in patients with PFO.

The Association between Migraine and Types of Sleep Disorder.

Kim SJ[1,2], Han KT[3,4], Jang SY[5], Yoo KB[6], Kim SJ[7].

Background: Migraines gradually increase year by year, as does its burden. Management and prevention are needed to reduce such burdens. Previous studies have suggested that daily health behaviors can cause migraines. Sleep is a substantial part of daily life, and in South Korea, the average sleep duration is shorter than in other countries. Thus, this study focused on the increase of both diseases, and analyzed sleep disorders as a risk factor for migraines.

Methods: The data used in this study was that of the national health insurance service (NHIS) national sample cohort. We used a matched cohort study design that matched non-patients based on patients with sleep disorders, and included 133,262 patients during 2012–2015. We carried out a survival analysis using a Cox proportional hazard model with time-dependent covariates to identify the association between migraines and sleep disorders.

Results: Approximately 11.72% of patients were diagnosed with migraines. Sleep disorders were positively correlated with the diagnosis of migraine (Hazard Ratio, 1.591; *p* < 0.0001). By the types of sleep disorder, patients who were diagnosed as having insomnia, rather than other types of sleep disorder, had the greatest associations with migraine. The associations were greater for males, people with lower income, the elderly population, and patients with mild comorbid conditions.

Conclusion: This study provides evidence that migraine is associated with sleep disorders, especially insomnia. Based on these findings, healthcare professionals and policy makers have to reconsider the present level of insurance coverage for sleep medicine, recognize the risk of sleep-related diseases and educate patients about the need for appropriate care.

HEADACHE and MIGRAINE (Continued)

My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed.

Martelletti P[1,2], Schwedt TJ[3], Lanteri-Minet M[4], Quintana R[5], Carboni V[6], Diener HC[7], Ruiz de la Torre E[8], Craven A[9], Rasmussen AV[10], Evans S[11], Laflamme AK[12], Fink R[12], Walsh D[13], Dumas P[14], Vo P[12].

BACKGROUND: Migraine is associated with many debilitating symptoms that affect daily functioning. My Migraine Voice is a large global cross-sectional study aimed at understanding the full burden and impact of migraine directly from patients suffering from ≥4 monthly migraine days (MMDs) with a history of prophylactic treatment failure.

METHODS: This study was conducted worldwide (31 countries across North and South Americas, Europe, the Middle East and Northern Africa, and the Asia-Pacific region) using an online survey administered to adults with migraine who reported ≥4 MMDs in the 3 months preceding survey administration, with pre-specified criteria of 90% having used preventive migraine treatment (80% with history of ≥1 treatment failure). Prophylactic treatment failure was defined as a reported change in preventive medication by individuals with migraine for any reason, at least once.

RESULTS: In total, 11,266 individuals participated in the survey. Seventy-four percent of the participants reported spending time in darkness/isolation due to migraine (average: 19 h/month). While 85% of all respondents reported negative aspects of living with migraine (feeling helpless, depressed, not understood), sleeping difficulties (83%), and fear of the next attack (55%), 57% shared ≥1 positive aspect (learning to cope, becoming a stronger person). Forty-nine percent reported feeling limited in daily activities throughout all migraine phases. Migraine impact on professional, private, or social domains was reported by 87% of respondents (51% in all domains). In the previous 12 months, 38% of respondents had visited the emergency department (average: 3.3 visits), whereas 23% stayed in hospital overnight (average: 3.2 nights) due to migraine.

CONCLUSIONS: The burden of migraine is substantial among this cohort of individuals with at least 4 migraine days per month and for whom at least 1 preventive migraine treatment had failed. Interestingly, respondents reported some positive aspects in their migraine journey; the greater resilience and strength brought on by coping with migraine suggests that if future treatments could address existing unmet needs, these individuals with migraine will be able to maximize their contribution to society.

CHRONIC PAIN

Use of Complementary and Integrated Health: A Retrospective Analysis of U.S. Veterans with Chronic Musculoskeletal Pain Nationally.

Taylor SL[1,2], Herman PM[3], Marshall NJ[4], Zeng Q[5,6], Yuan A[1], Chu K[1], Shao Y[5], Morioka C[7], Lorenz KA[4].

OBJECTIVE: To partially address the opioid crisis, some complementary and integrative health (CIH) therapies are now recommended for chronic musculoskeletal pain, a common condition presented in primary care. As such, healthcare systems are increasingly offering CIH therapies, and the Veterans Health Administration (VHA), the nation's largest integrated healthcare system, has been at the forefront of this movement. However, little is known about the uptake of CIH among patients with chronic musculoskeletal pain. As such, we conducted the first study of the use of a variety of nonherbal CIH therapies among a large patient population having chronic musculoskeletal pain.

MATERIALS AND METHODS: We examined the frequency and predictors of CIH therapy use using administrative data for a large retrospective cohort of younger veterans with chronic musculoskeletal pain using the VHA between 2010 and 2013 (n = 530,216). We conducted a 2-year effort to determine use of nine types of CIH by using both natural language processing data mining methods and administrative and CPT4 codes. We defined chronic musculoskeletal pain as: (1) having 2+ visits with musculoskeletal diagnosis codes likely to represent chronic pain separated by 30-365 days or (2) 2+ visits with musculoskeletal diagnosis codes within 90 days and with 2+ numeric rating scale pain scores ≥4 at 2+ visits within 90 days.

RESULTS: More than a quarter (27%) of younger veterans with chronic musculoskeletal pain used any CIH therapy, 15% used meditation, 7% yoga, 6% acupuncture, 5% chiropractic, 4% guided imagery, 3% biofeedback, 2% t'ai chi, 2% massage, and 0.2% hypnosis. Use of any CIH therapy was more likely among women, single patients, patients with three of the six pain conditions, or patients with any of the six pain comorbid conditions.

CONCLUSIONS: Patients appear willing to use CIH approaches, given that 27% used some type. However, low rates of some specific CIH suggest the potential to augment CIH use.

CHRONIC PAIN (Continued)

Mental health functioning and severity of cannabis withdrawal among medical cannabis users with chronic pain.

Perron BE[1], Holt KR[2], Yeagley E[3], Ilgen M[3] .

PURPOSE: To describe patterns of cannabis withdrawal among a large sample of those who use medical cannabis and test the association between withdrawal symptomology and functioning.

PROCEDURES: Adults ages 21 and older (N = 801) who were seeking medical cannabis certification (either for the first time or as a renewal) for chronic pain at medical cannabis clinics in southern Michigan completed baseline measures of cannabis use, withdrawal symptomology, functioning and other related constructs. Patients were included in the current study if they endorsed using cannabis at least weekly over the past three months. Of the persons in the baseline sample (N = 801), 83% endorsed using cannabis at this level of frequency and duration (N = 665).

FINDINGS: Approximately two-thirds of the sample (67.8%) reported at least one moderate or severe withdrawal symptom. The most commonly observed symptom was sleep difficulties (50.3%), followed by anxiety (27.8%), irritability (26.7%), and appetite disturbance (25.2%). Patients with low mental functioning had significantly higher rates of withdrawal symptom endorsement than patients with high mental functioning. However, no association was observed between physical functioning and withdrawal symptom endorsement. These patterns of association were consistent in multivariate analyses that controlled for other potentially confounding variables.

CONCLUSIONS: Cannabis withdrawal symptomology is highly prevalent among patients who use medical cannabis at least three times a week. Helping patients recognize the association between poorer functioning and withdrawal may be an effective way to highlight potentially negative consequences of regular and moderate heavy use.

Effects of Opioids and Nonsteroidal Anti-Inflammatory Drugs on Chronic Low Back Pain and Related Measures: Results from the PRECISION Pain Research Registry.

Licciardone JC, Gatchel RJ, Aryal S.

Measuring treatments used by 202 patients with chronic low back pain in the PRECISION Pain Research Registry, this study determined the associations of opioid and nonsteroidal anti-inflammatory drug (NSAID) therapy with clinical status. More than one-fourth of patients did not use nonpharmacologic treatments for low back pain. Patients age 50-59 and 60-79 years old were more likely to use opioids than younger patients. Patients using opioids reported greater pain and back-related disability than did patients using NSAIDs. Patients concurrently using opioids and NSAIDs reported greater back-related disability and poorer quality of life than did patients using no or other pharmacologic therapy. No significant associations between pharmacologic therapy and clinical status remained after controlling for potential confounders. Neither opioids nor opioids combined with NSAIDs were more effective than just NSAIDs. Greater use of nonpharmacologic therapies and better second-line, nonopioid pharmacologic therapies appear necessary for more effective treatment of chronic low back pain.

CHRONIC PAIN (Continued)

Facilitators and Barriers to Implementation of a Peer Support Intervention for Patients with Chronic Pain: A Qualitative Study.

Shue SA[1,2], McGuire AB[2,3], Matthias MS[2,4,5,6].

Objective: Pain self-management information and support, delivered by peers, are a potentially useful approach to help patients who are struggling to manage their chronic pain. Before implementation into clinical settings, it is important to understand factors that may influence the success of implementation. The purpose of this study was to explore facilitators and barriers to implementation of peer support for chronic pain.

Design: Semistructured interviews were conducted with clinicians who provide care to patients with chronic pain, regarding their perceptions of the proposed peer support intervention.

Setting: A single US Veterans Affairs Medical Center.

Subjects: Using maximum variation sampling, 15 providers were interviewed (11 women, four men). Clinicians' disciplines included primary care, physical therapy, nursing, clinical psychology, social work, and pharmacy.

Results: Findings indicated that clinicians 1) had an overall positive perception of the intervention; 2) had specific intervention outcomes they wanted for patients; 3) anticipated that the intervention could positively influence their role; 4) anticipated barriers to intervention participation and maintenance; and 5) had concerns regarding peer coach selection. Findings are discussed in the context of the Consolidated Framework for Implementation Research.

Conclusions: Understanding clinician perceptions of a peer support intervention is critical for successful implementation. The feedback collected in this study will facilitate implementation of the intervention on a broader scale, allowing more patients to benefit.

OTHER RESEARCH OF INTEREST

Gulf War and Health. Volume 11: Generational Health Effects of Serving in the Gulf War (2018)

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on Gulf War and Health.

Report at a Glance: Report highlights (PDF). Summary table (PDF).

For the United States, the 1991 Persian Gulf War was a brief and successful military operation with few injuries and deaths. However, soon after returning from duty, a large number of veterans began reporting health problems they believed were associated with their service in the Gulf. At the request of Congress, the National Academies of Sciences, Engineering, and Medicine has been conducting an ongoing review of the evidence to determine veterans' long-term health problems and potential causes.

Some of the health effects identified by past reports include post-traumatic stress disorders, other mental health disorders, Gulf War illness, respiratory effects, and self-reported sexual dysfunction. Veterans' concerns regarding the impacts of deployment-related exposures on their health have grown to include potential adverse effects on the health of their children and grandchildren. These concerns now increasingly involve female veterans, as more women join the military and are deployed to war zones and areas that pose potential hazards.

Gulf War and Health: Volume 11 evaluates the scientific and medical literature on reproductive and developmental effects and health outcomes associated with Gulf War and Post-9/11 exposures, and designates research areas requiring further scientific study on potential health effects in the descendants of veterans of any era.

OTHER RESEARCH OF INTEREST (Continued)

Posttraumatic Stress Disorder Symptoms, Temperament, and the Pathway to Cellular Senescence.

Connolly SL[1], Stoop TB[2], Logue MW[2,3], Orr EH[4,5], De Vivo I[4,5], Miller MW[2,3], Wolf EJ[2,3].

Traumatic stress is thought to be associated with shortened telomere length (TL) in leukocytes, an age-related marker of increased risk for cellular senescence, although findings thus far have been mixed. We assessed associations between posttraumatic stress disorder (PTSD) symptom severity, temperament, and TL in a sample of 453 White, non-Hispanic, middle-aged, trauma-exposed male and female veterans and civilians. Given that prior research has suggested an association between PTSD and accelerated cellular age, we also examined associations between TL and an index of accelerated cellular age derived from DNA methylation data (DNAm age). Analyses revealed that, controlling for chronological age, PTSD was not directly associated with TL but rather this association was moderated by age, β = -.14, p = .003, ΔR^2 = .02. Specifically, PTSD severity evidenced a stronger negative association with TL among relatively older participants ($\geq$ 55 years of age). In a subset of veterans with data pertaining to temperament (n = 150), positive emotionality, and, specifically, a drive toward achievement, β = .26, p = .002, ΔR^2 = .06, were positively associated with TL. There was no evidence of an association between age-adjusted TL and accelerated DNAm age. Collectively, these results indicate that older adults may be more vulnerable to the negative health effects of PTSD but that traits such as achievement, resilience, and psychological hardiness may be protective. These findings underscore the importance of identifying reliable biomarkers of cellular aging and senescence and of determining the biological mechanisms that contribute to stress-related disease and decline.

The Burden of Frailty Among U.S. Veterans and Its Association With Mortality, 2002-2012.

Orkaby AR[1,2,3], Nussbaum L[2], Ho YL[2], Gagnon D[2,4], Quach L[2,5], Ward R[2], Quaden R[2], Yaksic E[2], Harrington K[2,6], Paik JM[1,7], Kim DH[8,9], Wilson PW[2,10,11,12], Gaziano MJ[2,3], Djousse L[2,3], Cho K[2,3], Driver JA[1,2,3].

Background: Frailty is a key determinant of clinical outcomes. We sought to describe frailty among U.S. Veterans and its association with mortality.

Methods: Nationwide retrospective cohort study of regular Veterans Affairs (VA) users, aged at least 65 years in 2002-2012, followed through 2014, using national VA administrative and Medicare/Medicaid data. A frailty index (FI) for VA (VA-FI) was calculated using the cumulative deficit method. Thirty-one age-related deficits in health from diagnostic and procedure codes were included and were updated biennially. Survival analysis assessed associations between VA-FI and mortality.

Results: A VA-FI was calculated for 2,837,152 Veterans over 10 years. In 2002, 36.7% were non-frail (FI = 0-0.10), 33.3% were pre-frail (FI = 0.11-0.20), 18.6% were mildly frail (FI = 0.21-0.30), 8.0% were moderately frail (FI = 0.31-0.40), and 3.4% were severely frail (FI > 0.40). From 2002 to 2012, the prevalence of moderate frailty increased to 12.6%and severe frailty to 12.3%. Frailty was strongly associated with survival and was independent of age, sex, race, and smoking; the VA-FI better predicted mortality than age alone. Although prevalence of frailty rose over time, compared to non-frail Veterans, 2 years' hazard ratios (95% confidence intervals) for mortality declined from a peak in 2004 of 2.05 (2.02-2.09), 3.72 (3.67, 3.78), 6.43 (6.33-6.53), and 11.11 (10.93-11.29) for pre-frail, mildly, moderately, and severely frail, respectively, to 1.53 (1.51, 1.55), 2.48 (2.44-2.51), 3.96 (3.90-4.01), 6.98 (6.89-7.07) in 2014. At every frailty level, risk of mortality was lower for women versus men and higher for blacks versus whites.

Conclusions: Frailty affects 3 of every 10 U.S. Veterans aged at least 65 years, and is strongly associated with mortality. The VA-FI could be used to more accurately estimate life expectancy and individualize care for Veterans.

OTHER RESEARCH OF INTEREST (Continued)

Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators.

BACKGROUND: The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017) includes a comprehensive assessment of incidence, prevalence, and years lived with disability (YLDs) for 354 causes in 195 countries and territories from 1990 to 2017. Previous GBD studies have shown how the decline of mortality rates from 1990 to 2016 has led to an increase in life expectancy, an ageing global population, and an expansion of the non-fatal burden of disease and injury. These studies have also shown how a substantial portion of the world's population experiences non-fatal health loss with considerable heterogeneity among different causes, locations, ages, and sexes. Ongoing objectives of the GBD study include increasing the level of estimation detail, improving analytical strategies, and increasing the amount of high-quality data.

METHODS: We estimated incidence and prevalence for 354 diseases and injuries and 3484 sequelae. We used an updated and extensive body of literature studies, survey data, surveillance data, inpatient admission records, outpatient visit records, and health insurance claims, and additionally used results from cause of death models to inform estimates using a total of 68 781 data sources. Newly available clinical data from India, Iran, Japan, Jordan, Nepal, China, Brazil, Norway, and Italy were incorporated, as well as updated claims data from the USA and new claims data from Taiwan (province of China) and Singapore. We used DisMod-MR 2.1, a Bayesian meta-regression tool, as the main method of estimation, ensuring consistency between rates of incidence, prevalence, remission, and cause of death for each condition. YLDs were estimated as the product of a prevalence estimate and a disability weight for health states of each mutually exclusive sequela, adjusted for comorbidity. We updated the Socio-demographic Index (SDI), a summary development indicator of income per capita, years of schooling, and total fertility rate. Additionally, we calculated differences between male and female YLDs to identify divergent trends across sexes. GBD 2017 complies with the Guidelines for Accurate and Transparent Health Estimates Reporting.

FINDINGS: Globally, for females, the causes with the greatest age-standardised prevalence were oral disorders, headache disorders, and haemoglobinopathies and haemolytic anaemias in both 1990 and 2017. For males, the causes with the greatest age-standardised prevalence were oral disorders, headache disorders, and tuberculosis including latent tuberculosis infection in both 1990 and 2017. In terms of YLDs, low back pain, headache disorders, and dietary iron deficiency were the leading Level 3 causes of YLD counts in 1990, whereas low back pain, headache disorders, and depressive disorders were the leading causes in 2017 for both sexes combined. All-cause age-standardised YLD rates decreased by 3·9% (95% uncertainty interval [UI] 3·1-4·6) from 1990 to 2017; however, the all-age YLD rate increased by 7·2% (6·0-8·4) while the total sum of global YLDs increased from 562 million (421-723) to 853 million (642-1100). The increases for males and females were similar, with increases in all-age YLD rates of 7·9% (6·6-9·2) for males and 6·5% (5·4-7·7) for females. We found significant differences between males and females in terms of age-standardised prevalence estimates for multiple causes. The causes with the greatest relative differences between sexes in 2017 included substance use disorders (3018 cases [95% UI 2782-3252] per 100 000 in males vs s1400 [1279-1524] per 100 000 in females), transport injuries (3322 [3082-3583] vs 2336 [2154-2535]), and self-harm and interpersonal violence (3265 [2943-3630] vs 5643 [5057-6302]).

INTERPRETATION: Global all-cause age-standardised YLD rates have improved only slightly over a period spanning nearly three decades. However, the magnitude of the non-fatal disease burden has expanded globally, with increasing numbers of people who have a wide spectrum of conditions. A subset of conditions has remained globally pervasive since 1990, whereas other conditions have displayed more dynamic trends, with different ages, sexes, and geographies across the globe experiencing varying burdens and trends of health loss. This study emphasises how global improvements in premature mortality for select conditions have led to older populations with complex and potentially expensive diseases, yet also highlights global achievements in certain domains of disease and injury.

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