

# BONES & BRAIN

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## GENICULAR ARTERY EMBOLIZATION FOR KNEE OSTEOARTHRITIS

Neovascularization is common in painful musculoskeletal conditions. In chronic musculoskeletal pain, neovessels are thought to be part of a pathological response that sustains inflammation and produces pain. Transcatheter arterial embolization (TAE) has been proposed to disrupt the dysregulated inflammatory response by reducing the vascular transport of proinflammatory mediators and stimulation of sensory nerves. This study was designed to better understand the effects of TAE on patients with recalcitrant knee osteoarthritis (KOA).

This triple blind, randomized trial included adults, 18 to 75 years of age, with grade II knee OA (Kellgren-Lawrence scale) with moderate to severe unilateral knee pain that was resistant to at least six months of conservative treatment. Those randomized to a treatment group underwent TAE of one or more genicular arteries, while a control group received a blinded sham procedure. The primary outcome variable was knee pain, measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) up to 12 months after the procedure.

Of the 59 participants, 52 completed the physical performance measures at six months, and 47 at 12 months. Compared to baseline, the median KOOS pain scores at 12 months improved in the control group by 29.4% and the intervention group by 41.3%. At 12 months, the proportions of participants taking analgesia were 48% in the control group and 24% in the intervention group ( $p=0.057$ ). A subgroup analysis revealed that those who underwent embolization of all of their genicular arteries had significantly better outcomes than the placebo group across all KOOS scales.

**Conclusion:** This small study of patients with osteoarthritis of the knee found that complete embolization of

all genicular arteries could produce beneficial effects.

Landers, S., et al. Genicular Artery Embolization for Early-Stage Osteoarthritis: Results from a Triple Blind Single Center Randomized Controlled Trial. *Bone Joint Open*. 2023, March; 4(3): 158-167.

## MOTORIC COGNITIVE RISK SYNDROME AND CHRONIC PAIN

The motoric cognitive risk (MCR) syndrome is a pre-dementia condition defined as subjective cognitive concerns and slow gait speed. Prospective studies have shown that MCR is an independent risk factor for dementia. This study was designed to determine whether a correlation exists between chronic pain and the development of MCR.

Subjects were recruited from among participants in the China Health and Retirement Longitudinal Study (CHARLS). The sample included 3,711 patients  $\geq 60$  years of age, without dementia or mobility disability, including 1,413 with chronic pain. A self-report memory loss questionnaire was administered, with the participants asked to rate their memory function as excellent, very good, good, fair, or poor. Those responding fair or poor were identified as having subjective cognitive concerns.

Of those studied, 482 (13%) had a diagnosis of MCR at baseline. Older adults with chronic pain were significantly more likely than were those without chronic pain to be diagnosed with MCR (Odds Ratio (OR) 1.397  $p<0.001$ ). In the longitudinal analysis 13.8% were newly diagnosed with MCR. An adjusted analysis found that the risk of developing MCR during the four year follow-up was greater among those with chronic pain, with a hazard ratio (HR) of 1.56. ( $p<0.001$ ).

**Conclusion:** This study suggests that motoric cognitive risk syndrome may be exacerbated by chronic pain.

Liang, H., et al. Chronic Pain Increases the Risk of Motoric Cognitive Risk Syndrome at Four Years of Follow-Up: Evidence from The China Health and Retirement Longitudinal Study. *Euro J Neurol*. 2023, April; 30(4): 831-838.

## PROGRESS IN ELIMINATING HIV AS A GLOBAL PUBLIC HEALTH THREAT

The United States President's Emergency Plan for AIDS Relief (PEPFAR) was announced in January of 2003. The PEPFAR was designed to end the AIDS epidemic as a global threat by 2030. This study reviewed the progress of this program.

The PEPFAR was designed to strengthen the ability of partner countries to deliver effective, efficient, and sustainable health care, by building infrastructure, workforce, and country-level expertise. In addition, direct funding for antiretroviral therapy (ART) was provided. Data were gathered for population viral load suppression rates by gender and age group (15 to 24, 25 to 34, 35 to 49, and 50 years or older) for six countries (Eswatini, Lesotho, Malawi, Uganda, Zambia, and Zimbabwe), all of which completed two surveys during 2015 through 2021. To indicate the effectiveness of the intervention the population viral load suppression rate was calculated as the number of persons with HIV infection with viral load suppression ( $<1,000$  HIV copies per mL of blood) among all persons identified with HIV infection.

Data from 2004 through 2022 demonstrated that the number of people with HIV infection who were receiving PEPFAR-supported ART increased from 66,552 to 20,166,110 in 54 countries. During 2015 through 2022, the overall viral load suppression rate increased from 24% (2,109,749 of 8,806,300 eligible persons) to 80% (14,875,130 of 18,573,406). During 2015 through 2022, the viral load suppression rate increased from 80% to 95%.

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**Conclusion:** This study found that, since the onset of the PEPFAR program in 2004, 20 million people with HIV infection worldwide have received ART, with viral suppression rates in 2022 reaching 95%.

Chun, H., et al. *Vital Signs: Progress toward Eliminating HIV as a Global Public Health Threat through Scale-Up of Antiretroviral Therapy and Health System Strengthening Supported by the U.S. President's Emergency Plan for AIDS Relief-Worldwide, 2004-2022. MMWR Morb Mortal Wkly Rep.* 2023, March 24; 72(12): 317-324.

### **GROWTH FACTOR INJECTIONS FOR KNEE OSTEOARTHRITIS**

Osteoarthritis (OA) is a disease of the entire joint, including cartilage, subchondral bone, synovium, menisci, and ligaments. The mechanism appears to be an inflammatory process, with insufficient anabolic factors combined with an increase in catabolic factors, leading to an overexpression of matrix degrading proteases. This study assessed the clinical efficacy of growth factor injections for patients with knee OA (KOA).

This prospective, blinded, placebo-controlled trial included adults with clinical features of KOA, with x-rays demonstrating K-L grade II or III. Patients were randomized to receive three monthly injections of 3cc normal saline (placebo), or autologous growth factor concentrate (GFC), created using the commercially available plasma rich in growth factors (PRGF) "OSSINEXT GFC therapy kit". The primary outcome measure was the Visual Analog Scale (VAS) for pain and the Western Ontario and McMaster universities arthritis index (WOMAC). Levels of Collagen 2-1 (Coll2-1) were obtained as a measure of collagen degradation.

Data were analyzed for 58 patients. Compared to the placebo group, significantly better improvements in VAS scores were noted in the treatment group at three, six, and 12 months ( $p < 0.001$  for all comparisons). The treatment group also obtained better WOMAC scores at three, six, and twelve months ( $p < 0.001$  for all). Improvement in the Coll2-1 levels was found only in the treatment group at 12 months ( $p < 0.001$ ).

**Conclusion:** This study found that serial injections of growth factor concentrate provided improvement in pain and function and a significant

decrease in serum markers of cartilage degradation at 12 months.

Saraf, A., et al. Serial Intraarticular Injections of Growth Factor Concentrate in Knee Osteoarthritis: A Placebo-Controlled, Randomized Study. *J Orthop.* 2023, March; 37: 46-52.

### **BOTULINUM TOXIN FOR KNEE OSTEOARTHRITIS**

Botulinum toxin A (Btx-A) has been shown to have inhibitory effects on neuropeptide secretion and a suppression of inflammation. This study investigated the efficacy and safety of this medication for the management of knee osteoarthritis (KOA).

The medical literature was reviewed for studies involving adults with KOA treated with an intra-articular injection at the knee joint using a 100-200 IU dose. In addition, the studies were required to have a comparison group that received injections containing placebo such as 0.9% saline solution or education only without any injections. The review produced six studies, including a total of 446 patients.

A pooled analysis demonstrated that, compared to the control group, intraarticular injections with Btx-A resulted in a greater improvement in VAS pain scores from baseline to four weeks ( $p = 0.007$ ). In addition, greater improvements were noted in the Btx-A group in Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores for up to four weeks ( $p = 0.03$ ).

**Conclusion:** This pooled analysis of randomized, controlled trials of Btx-A for the treatment of osteoarthritis of the knee found significant improvement in pain and function within four weeks of the injections.

Ismiarto, Y., et al. Efficacy and Safety of Intraarticular Botulinum Toxin A Injection for Knee Osteoarthritis: A Systematic Review, Meta-Analysis, and Meta-Regression of Clinical Trials. *JBJS Open Access.* 2023, January-March; 8(1):e22.00121.

### **BLOOD ANTIOXIDANT LEVELS AND FEMORAL NECK STRENGTH**

Osteonecrosis of the femoral head (ONFH) increases the risk of traumatic and non-traumatic fracture. Several studies have suggested that antioxidants contribute to a lower risk of osteoporosis. This study assessed the effect of blood levels of

antioxidants on femoral neck strength.

Data were obtained from the Midlife in the United States (MIDUS) study, designed to investigate the psychosocial and behavioral factors involved in age-related health conditions among a national sample of Americans. The Biomarker Project recruited participants from the original cohort, measuring various biological indicators in blood, urine, saliva, and other biological samples from 2004 to 2009. Data from 878 participants were used for this study.

An assessment of femoral strength was conducted, with indices of femoral neck strength including a compressive strength index (CSI), calculated as  $BMD \times FNW/Weight$ , a bending strength index (BSI), calculated as  $BMD \times FNW^2 / (FNAL \times Weight)$ , and an impact strength index (ISI), calculated as  $(BMD \times FNW \times FNAL) / (Height \times Weight)$ . Blood levels of 10 antioxidant markers were obtained (total lutein, zeaxanthin, beta-cryptoxanthin, 13-cis-beta-carotene, alpha-carotene, trans-beta-carotene, total lycopene, gamma-tocopherol, alpha-tocopherol, and retinol).

Blood levels of six antioxidants were positively associated with CSI, BSI, or ISI. In addition, gamma-tocopherol and alpha-tocopherol levels were negatively associated with CSI, BSI, or ISI. A regression analysis revealed that only elevated blood zeaxanthin levels were positively and significantly correlated with CSI ( $p=0.045$ ), BSI ( $p=0.037$ ), and ISI ( $p=0.045$ ).

**Conclusion:** This cross-sectional analysis found that increasing blood levels of antioxidants, especially zeaxanthin, may increase femoral neck strength.

Niu, P., et al. Associations between Blood Antioxidant Levels and Femoral Neck Strength. **BMC Musculoskel Dis.** 2023. <https://doi.org/10.1186/s12891-023-06370-5>.

### VITAMIN D INSUFFICIENCY AND DEMENTIA

Dementia affects six percent of those  $\geq 65$  years of age and is expected to become more prevalent as the population of the world increases. As several studies have demonstrated that metabolites of vitamin D induce the removal of amyloid beta proteins, and have other neuroprotective processes, this study was designed to determine the association between serum levels of 25(OH)D and the onset of dementia.

This retrospective cohort study included data from the electronic medical records of Clalit Health Services, which insures 53% of the population of Israel. All patients with at least one recorded 25(OH)D result were included. Follow-up continued until the occurrence of dementia of any kind, death, or the end of the study on July 1, 2019. The association between mean serum vitamin D level and dementia was evaluated using binary logistic regression analysis.

Data were obtained from 4,278 adults, of whom 133 (three percent) received a diagnosis of dementia. Of those with dementia, 86% had vitamin D insufficiency ( $<75$  nmol/l), and 53% had vitamin D deficiency ( $<50$  nmol/l). In the fully adjusted multivariate analysis, compared to those with normal serum levels of vitamin D, the adjusted odds ratio (OR) of a diagnosis of dementia was 1.8 for those with vitamin D insufficiency ( $<75$  nmol/l), 2.6 for those with vitamin D deficiency ( $<50$  nmol/l), and 2.7 for those with severe vitamin D deficiency ( $<25$  nmol/l).

**Conclusion:** This retrospective cohort study found that lower serum levels of vitamin D were associated with a higher incidence of dementia.

Kiderman, D., et al. Vitamin D Insufficiency Is Associated with Higher Incidence of Dementia: A Large, Community-Based, Retrospective, Cohort Study. **J Geriatr Psychiatry Neurol.** 2023 <https://doi.org/10.1177/0891988723116329>.

### DEMENTIA, EPILEPSY, AND CARDIOVASCULAR RISK

Epilepsy is a common neurologic condition that increases in incidence after 55 years of age. Studies have suggested that those with epilepsy may have an increased risk of dementia as they age. This study analyzed the risk of developing dementia across a wide range of neurologic conditions.

This cross-sectional study included data from the United Kingdom Biobank, targeting individuals 38 to 72 years of age. All underwent physiologic measurement and cognitive testing, with biological samples provided. All dementia cases were identified during longitudinal follow-up. Cardiovascular risk was assessed using known risk factors, with the patients placed in low or high-risk groups. Computerized cognitive testing was used to evaluate cognition and dementia.

The data analysis included 495,149 individuals with a mean age of 57.5 years and a mean follow-up of 12 years. During the follow-up, the adjusted hazard ratio (HR) for incident dementia was 4.02 for participants with focal epilepsy, 2.56 for patients with stroke, and 1.02 for patients with migraine. Those with focal epilepsy and high cardiovascular risk had a dramatically increased risk of developing dementia compared to those without epilepsy and low cardiovascular risk (HR 13.66).

**Conclusion:** This study found that epilepsy was associated with a significant risk of developing dementia, which was magnified substantially by cardiovascular risk factors.

Tai, X., et al. Association of Dementia Risk with Focal Epilepsy and Modifiable Cardiovascular Risk Factors. **JAMA Neurol.** 2023 [doi: 10.1001/jamaneurol.2023.0339](https://doi.org/10.1001/jamaneurol.2023.0339).

### TRANSCRANIAL DIRECT CURRENT STIMULATION FOR SUBACUTE APHASIA

After stroke, particularly left hemisphere stroke, aphasia is a common symptom. The SLISSE (Stimulating Language in Subacute Stroke) was conducted to determine whether transcranial direct current stimulation (tDCS) can augment computer-delivered language therapy for improving picture naming and discourse.

The subjects were patients with a left hemisphere ischemic stroke within three months of recruitment. All were screened using the Western Aphasia Battery-Revised and the National Institutes of Health Stroke Scale. Descriptions of the Cookie Theft picture on the National Institutes of Health Stroke Scale were analyzed for content units (CU) and syllables/CU. Both groups received standard speech and language pathology care (fifteen 45-minute sessions of naming treatment) and were randomized to receive either active A-tDCS ( $n=30$ ) or sham S-tDCS ( $n=28$ ) delivered during the first 20 minutes. The sessions occurred over three to five weeks. The primary outcome variable was the change in the number of correctly named items on the Philadelphia Naming Test (PNT).

Compared to baseline, at five weeks, the improvement in CU was 5.42 in the active group, and 1.42 in the sham group ( $p=0.0196$ ). Greater gains in efficiency of discourse were

noted in the active group as compared to the sham group at five weeks ( $p=0.0164$ ) and 20 weeks follow-up ( $p=0.0011$ ). No significant changes between groups were found in the accuracy of naming untrained pictures at five or 20 weeks.

**Conclusion:** This study of patients with ischemic stroke found that tDCS, combined with speech therapy, did not improve picture naming, but did improve the content and efficiency of the picture description.

Stockbridge, M., et al. Transcranial Direct-Current Stimulation in Subacute Aphasia: A Randomized, Controlled Trial. *Stroke*. 2023, April;54(4): 912-920.

### CRANIAL MAGNETIC STIMULATION IN NON-RESPONSIVE PATIENTS

Disorders of consciousness resulting from severe brain injury encompass a wide spectrum of conditions, ranging from coma to vegetative state/unresponsive wakefulness syndrome (VS/UWS) to minimally conscious state (MCS). Given that several studies have demonstrated the efficacy of repetitive transcranial magnetic stimulation (rTMS) to modulate cortical excitability, this study assessed the efficacy of rTMS for patients in VS/UWS.

This crossover, randomized, double-blind, sham-controlled trial included 24 patients, 18 to 70 years of age, with acquired brain injuries within the past year who were diagnosed as VS/UWS for more than 28 days. Participants were randomized to receive ten sessions of either sham or active rTMS, targeting the left posterior parietal cortex (PPC). After a 10-day washout period, the treatment conditions were reversed. All patients underwent assessment with the JFK Coma Recovery Scale-Revised (CRS-R) before and after the treatment.

Compared to those in the sham treatment group, those receiving active rTMS had significantly greater improvement in the CRS-R total score ( $p=0.009$ ). Of the 20 patients who responded to the rTMS, eight progressed to a minimally conscious state. Of these, two patients improved on the motor subscore (functional object use and pain location), and six patients improved on the visual subscore (visual pursuit).

**Conclusion:** This study of patients with traumatic brain injury in a vegetative state/unresponsive

wakefulness syndrome found that repetitive transcranial magnetic stimulation could improve functional recovery.

Xu, C., et al. Repetitive Transcranial Magnetic Stimulation over the Posterior Parietal Cortex Improves Functional Recovery in Non-Responsive Patients. A Crossover, Randomized, Double-Blind, Sham Controlled Study. *Front Neurol*. 2023, Feb 16;14:1059789. doi: 10.3389/fneur.2023.1059789.

### OCCUPATIONAL INHALABLE AGENTS AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune joint disorder affecting up to one percent of the global population. Recognized risk factors for developing RA have included human leucocyte antigen class II shared epitope (HLA-SE) alleles and external exposures such as tobacco smoke. This study examined the associations between multiple occupational inhalable exposures and the risk of RA.

Data were obtained using the large case-control study, Epidemiological Investigation of RA (EIRA). This study included adults in southern/central regions of Sweden. Those newly diagnosed with RA were matched with controls selected from a nationwide population registry. Data collected included demographics, work history, lifestyle, and blood samples. A job-exposure matrix (JEM) was applied to assess the prevalence and concentration of 32 inhalable agents. A Genetic Risk Score (GRS) was calculated, with the subjects labelled as low or high genetic risk. The results were stratified by the presence of anticitrullinated protein antibodies (ACPA).

Data were collected from 4,251 RA cases and 6,934 controls. Exposure to one of the 32 inhalable agents occurred in 73% of the ACPA-positive cases, 72% of the ACPA-negative cases, and 67% of the controls. Exposure to any of the agents was associated with an increased risk of RA (Odds Ratio (OR) 1.21). The strongest associations for those with ACPA negative RA were found for quartz dust, followed by asbestos and detergents. The risk increased with a greater number and duration of exposures ( $p<0.001$  for both). Compared to those with no exposure, the odds ratio for those with triple exposure (those exposed to any

occupational inhalable agent, smokers, and those who were ACPA-positive), was 18.22.

**Conclusion:** This study of patients in southern Sweden found that occupational inhalable agents may act as important environmental triggers in the development of rheumatoid arthritis.

Tang, B., et al. Occupational Inhalable Agents Constitute Major Risk Factors for Rheumatoid Arthritis, particularly in the Context of Genetic Predisposition and Smoking. *Ann Rheum Dis*. 2023, March; 82: 316-322.

### NEUROCOGNITIVE DECLINE IN HIV

Given advances in antiretroviral therapy, people with HIV are now living longer. Though studies are inconclusive, data do suggest accelerated neurocognitive aging among people with HIV (PLHIV). This study was designed to better understand the longitudinal changes in neurocognitive function among PLHIV.

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) program is a prospective, observational study, conducted at six academic medical centers in the United States. Baseline assessments were performed between 2003 and 2007, with follow-ups between 2015 and 2020. The 12-year trajectories were compared between those  $\geq 60$  and those  $<60$  years of age.

The subjects were 402 people diagnosed with HIV, with an average age of 43.7 years. The global cognitive score (GCS) was calculated by obtaining the Z score for each of the 15 cognitive tests, producing a regression-based average. The total CHARTER cohort demonstrated a modest neurocognitive decline over the 12-year follow-up, beyond what would be expected based on typical ageing. Using the baseline data, a multivariable analysis found that the variables most strongly and independently predicting a worse GCS over the 12 years included hypertension, chronic pulmonary disease, Beck's Depression Inventory (BDI)  $> 13$ , lifetime cannabis use disorder, higher serum hepatic aspartate transaminase and lower serum protein. A worse GCS over 12 years was not associated with baseline or 12-year HIV disease or treatment variables (AIDS diagnosis, nadir or current CD4+ T-cell count,

ART use, or HIV suppression in plasma or CSF).

**Conclusion:** This study using data from the CHARTER program found that people living with HIV have a greater decline in cognition over time, although this change is related to modifiable variables other than the HIV infection.

Heaton, R., et al. Twelve-Year Neurocognitive Decline in HIV Is Associated with Comorbidities, Not Age: A Charter Study. *Brain*. 2023, March; 146(3): 1121-1131.

### CARDIOMETABOLIC EFFECTS OF GOLF VERSUS NORDIC WALKING

Cardiovascular diseases (CVDs) remain the leading cause of mortality among the elderly. It is known that CVDs can be prevented by controlling key determinants of cardiometabolic markers through lifestyle modifications. This study compared the effects of a single bout of one of three different types of exercise on cardiometabolic markers.

The subjects were 25 healthy male golfers >65 years of age. All completed three different exercise trials in random order and at a self-selected pace. These included walking, golf (while pulling their golf clubs), and Nordic walking. On the morning of each exercise, the subjects underwent blood tests and blood pressure measurement and were fitted with biometric monitors.

All three exercises produced significant decreases in systolic blood pressure ( $p < 0.001$ ). Nordic walking and walking also resulted in significant decreases in diastolic blood pressure ( $p = 0.038$  and  $p = 0.022$ , respectively). Improvements in blood glucose were superior in the golf group as compared to walking and Nordic walking ( $p < 0.001$  for both). The average HR for golf ( $p = 0.050$ ) was significantly lower than those for the other exercises. The average exercise intensities during each trial were 61% in the golf group, 77% in the Nordic walking group, and 76% in the walking group.

**Conclusion:** This study, involving men over 65 years of age, compared the acute effects of Nordic walking, walking, and golf, finding that all three improved the cardiovascular profile, with golf found to have more positive effects on lipids and glucose.

Kettinen, J., et al. Comparative Effectiveness of Playing Golf to Nordic Walking and Walking on Acute Physiological Effects on

Cardiometabolic Markers In Healthy Older Adults: A Randomized Crossover Study. *BMJ Open Sport Exerc Med*. 2023; 9: e001474. doi: 10.1136/bmjsem-2022-0014.

### SLEEP WAKE DISTURBANCES AFTER STROKE

Stroke is a leading cause of long-term disability across the globe. Studies have shown that sleep loss and sleep-wake disturbances are risk factors for brain disorders and have a detrimental effect on the evolution and long-term outcome of these disorders. This study evaluated the effect of sleep-wake disturbance on subsequent cardio-cerebrovascular events following an ischemic stroke or a transient ischemic attack (TIA).

This prospective cohort study recruited consecutive patients admitted to two stroke centers with an acute ischemic stroke or a TIA. All were assessed with a sleep burden index (SBI) calculated using combined data from the Respiratory Event Index, the Insomnia Severity Index, the International Restless Legs Syndrome Study Group Rating Scale, and self-estimated sleep duration at three months post stroke. Sleep disordered breathing (SDB; apnea-hypopnea index [AHI]) was calculated using polysomnography. The primary endpoint was a composite of death from any cause, stroke, TIA, non-fatal myocardial infarction, unplanned hospitalization for heart failure, or for unstable angina.

Of the 437 patients, 70 primary endpoint events were recorded. The SBI was significantly higher in patients with a subsequent event compared to those without ( $p = 0.0003$ ). In a logistic regression, adjusting for age, sex and NIHSS score, the SBI was associated with a higher risk of subsequent cerebro-cardiovascular event or death ( $p = 0.0056$ ).

**Conclusion:** This study of patients with a stroke or transient ischemic event found that those with sleep wake disturbances have a higher risk of subsequent cardio or cerebrovascular events or death between three and 36 months.

Duss, S., et al. Multiple Sleep-Wake Disturbances after Stroke Predict an Increased Risk of Cardio-Cerebrovascular Events or Death: A Prospective Cohort Study. *Euro J Neurol*. Mar 13. doi: 10.1111/ene.15784.

### BRAIN RESILIENCE TO TAU PATHOLOGY

The mechanisms of resilience against tau pathology among individuals across the Alzheimer's disease (AD) spectrum are not well understood. This longitudinal study investigated the role of several demographic, biologic, and brain structural factors in cognitive and brain resilience to tau pathology.

This multicenter study included participants across five cohorts. All potential subjects were assessed with F-flortaucipir PET (tau-PET) scan, structural MRI, and neuropsychological assessments including the Mini-Mental State Examination (MMSE). The selected subjects were amyloid- $\beta$  ( $A\beta$ )-positive, with either mild cognitive impairment [MCI,  $n = 152$ ] or AD-type dementia ( $n = 219$ ) at the time of tau-PET. The  $A\beta$  status was determined either by cerebrospinal fluid or PET. The data were analyzed to determine the role of several demographic, biological and brain structural factors in yielding cognitive and brain resilience to tau pathology as measured with PET.

Data were analyzed for 366 individuals with an average age of 73.2 years and a mean follow-up of 18 months. Of these, 41.3% were diagnosed with MCI and 58.7% with AD dementia. The analysis found an association between higher baseline tau-PET levels and rate of cognitive decline (MMSE) which was adversely modified by older age ( $p = 0.032$ ), higher education level ( $p = 0.011$ ) and higher intracranial volume ( $p = 0.016$ ). Greater cortical thickness was associated with slower decline, independent of the tau burden. Higher education modified the negative impact of tau on cortical thinning.

**Conclusion:** This study of patients with mild cognitive impairment or Alzheimer's disease found that the progression of cognitive decline and tau pathology was slowed by higher levels of education.

Bocancea, D., et al. Determinants of Cognitive and Brain Resilience to Tau Pathology: A Longitudinal Analysis. *Brain*. 2023. doi: 10.1093/brain/awad100. Online ahead of print.

### PREVALENCE AND NATURAL HISTORY OF POST-STROKE DEPRESSION

Depression is the most common affective complication after stroke.

Post-stroke depression (PSD) is associated with impaired function, decreased quality of life, and increased mortality. This systematic review and meta-analysis provides an update concerning the prevalence and persistence of PSD.

A literature search was conducted for studies involving adults with a clinical diagnosis of stroke, which assessed for depression at a pre-specified time point. The first analysis was conducted to determine prevalence, with the second to determine the pooled estimates of depression within one-year post-stroke.

The meta-analysis included data from 77 studies, with 27,401 participants. The overall pooled estimates for the prevalence of PSD at any time point was 27%. The prevalence within one month was 30%, at six months was 22% and at 12 months was 29%. Among those assessed as depressed within three months of stroke, depression persisted at long term follow up in 53%.

**Conclusion:** This literature review and meta-analysis found that the pooled estimate of post-stroke depression was 27%, and that more than half of those diagnosed within three months will have persistent depression.

Liu, L., et al. Prevalence and Natural History of Depression after Stroke: A Systematic Review and Meta-Analysis of Observational Studies. *Plos Med.* 2023; 20(3): e1004200.

### LOSS OF CONSCIOUSNESS, CLINICAL RECOVERY, AND PERFORMANCE ON THE SCAT5

Most sports related concussions occur without a loss of consciousness (LOC). This study evaluated the importance of LOC on the recovery of athletes participating in the National Rugby League between 2017 and 2019.

During the 2017 to 2019 season, video surveillance was employed for all matches. When a potential concussion was noted, the players underwent a Head Injury Assessment, including the Sports Concussion Assessment Tool, Fifth Edition (SCAT5). A possible LOC was defined as video evidence of no protective action during the fall, unresponsiveness, or lying motionless. Sport-specific orientation and amnesia were assessed using the Five Maddocks Question.

Of all head impact events, 5.8% of those injured had a possible LOC,

with 26.7% of those with medically diagnosed concussions demonstrating a possible LOC. Comparing those with and those without LOC, no significant group differences were found in SCAT5 symptom endorsement, Standardized Assessment of Concussion (SAC) total scores, orientation, immediate recall, concentration, delayed recall, or total errors on the modified version of the Balance Error Scoring System (mBESS). The duration of possible LOC was not associated with the time to medical clearance for match play.

**Conclusion:** This study of rugby players found that over 25% of those diagnosed with concussion had evidence of a loss of consciousness. The finding of loss of consciousness did not correlate with time to medical clearance.

Iverson, G., et al. Examining Whether Loss of Consciousness is Associated with Worse Performance on the SCAT-5 and Slower Clinical Recovery after Concussion in Professional Athletes. *J Neurotrauma.* 2023; 40: 1-11.

### INFRARED STIMULATION OF THE CEREBRAL CORTEX

Infrared neural stimulation (INS) is a technology that stimulates neural tissue through the delivery of tiny heat pulses. This study examined the effect of INS on human cerebral cortex, in order to establish damage thresholds.

The subjects were five epileptic patients undergoing lobotomy for epilepsy. The cortical response to INS were assessed by delivering single pulse trains of INS with intensities from 0.2 to 0.8 joules per centimeter squared ( $J/cm^2$ ). These were delivered to the somatosensory cortex, with responses recorded via optical imaging. After the lobectomy the tissue underwent histological analysis.

The INS-induced responses were highly focal and led to a relative suppression of nearby cortical sites. Histological examination revealed damage thresholds. Within the tested intensity range, the relationship between INS intensity and response magnitude showed a strong linear correlation. When the INS radiant exposure exceeded  $0.6 J/cm^2$  damage was visible in layers 2/3 of the cortex, suggesting a damage threshold of  $0.6 J/cm^2$ .

**Conclusion:** This small study of patients undergoing surgical debridement as a treatment for epilepsy describes a correlation

between the strength of infrared neural stimulation and response magnitude, as well as thresholds for tissue damage.

Pan, L., et al. Infrared Neural Stimulation in Human Cerebral Cortex. *Brain Stimul.* 2023; 16: 418-430.

### ANSERINE BURSA TENDERNESS AND KNEE OSTEOARTHRITIS

Previous studies have reported an association between anserine bursa pain (ABP) and knee osteoarthritis (KOA). This study investigated whether the presence of ABP at baseline is associated with KOA outcome.

Data were obtained from the Osteoarthritis Initiative (OAI) database, a multicenter, observational study of KOA. Subjects were 4,696 individuals with clinical KOA and baseline ages ranging from 45 to 79 years. All were evaluated by radiographs, with the Western Ontario and McMaster University Osteoarthritis (WOMAC) pain score, and for ABP at baseline. Those with ABP were compared to those without over a four-year follow-up period.

The presence of ABP at baseline was associated with an increased risk of experiencing frequent knee pain ( $p<0.026$ ), and an elevated risk of total knee arthroplasty ( $p=0.044$ ). The progression of joint space narrowing was not associated with baseline ABP. Those with ABP were found to have worse WOMAC pain scores ( $p<0.001$ ), stiffness scores ( $p<0.001$ ), and functional scores ( $p<0.001$ ).

**Conclusion:** This study of patients with knee osteoarthritis found that the presence of pain at the anserine bursa is correlated with risk for total knee arthroplasty.

Xiong, T., et al. Anserine Bursa Palpation Tenderness Is a Risk Factor for Knee Osteoarthritis Progression and Arthroplasty: Data from the Osteoarthritis Initiative. *Clin Rheum.* 2023, February; 42(2):519-527.

### CHILDHOOD OBESITY AND OSTEOARTHRITIS

Obesity and osteoarthritis (OA) are two of the more pervasive medical issues globally. Several studies have suggested an association between obesity and OA in adults. This study reviewed the association between childhood obesity and OA.

This two-sample mendelian randomization (MR) analysis included data from several genome wide association studies (GWAS). Data analysis was limited to individuals of European descent. The summary level data on childhood obesity were obtained from a genome wide association meta-analysis conducted by the Early Growth Genetics Consortium, involving 13,848 European children. Primary outcome data were obtained from a publicly available GWAS dataset, built by the MRC Integrative Epidemiology Unit (MRC-IEU) consortium using the UK Biobank and contained 462,933 Europeans (38,472 cases and 424,461 controls) with 9,851,867 SNPs. Five different models, including the inverse variance weighted model (IVW), the weighted median estimator model (WME), the weighted model-based method (WM), the MR-Egger regression model (MER), and the MR-Robust Adjusted Profile Score (MRAPS) were applied in this MR analysis.

The analysis found that childhood obesity was causally associated with OA ( $p=8.12 \times 10^{-13}$ ) and a secondary MR analysis demonstrated that childhood obesity was causally associated with knee OA ( $p=3.30 \times 10^{-13}$ ) and hip OA ( $p=1.07 \times 10^{-4}$ ).

**Conclusion:** This mendelian regression study revealed a causal relationship between childhood obesity and osteoarthritis, especially true for knee osteoarthritis.

Cao, Z., et al. A Causal Relationship between Childhood Obesity and Risk of Osteoarthritis: Results from a Two-Sample Mendelian Randomization Analysis. *Ann Med.* 2022, December; 54(1): 1636-1645.

### DEPRESCRIBING MEDICATIONS FOR OLDER ADULTS FROM HOSPITALIZATION THROUGH POST-ACUTE CARE

Polypharmacy is prevalent among older hospitalized patients and is associated with adverse post-discharge outcomes. This study evaluated the efficacy of a patient centered, deprescribing intervention for those discharged to a post-acute care (PAC) facility.

The Shed-MEDS randomized, clinical trial recruited patients  $\geq 50$  years of age, scheduled for discharge to a PAC facility, each of whom had been prescribed  $\geq 5$  medications. Data extracted from the records included sociodemographics, medical diagnosis, and medications. The subjects were randomized to a usual

care group or to the Shed-MEDS intervention, which consisted of a pharmacist- or nurse practitioner-led, comprehensive medication review, with deprescribing actions initiated in the hospital and continued throughout the PAC facility stay. The primary outcome variables were the total medication counts at hospital and PAC discharge. The secondary variables were the change in potentially inappropriate medications (PIMs) and drug burden index (DBI).

Data were collected from the records of 372 patients with a mean age of 76.2 years. Compared to the control group, the intervention group was prescribed 14% fewer medications at PAC facility discharge ( $p < 0.001$ ) and 15% fewer medications at 90-day follow-up ( $p < 0.001$ ).

**Conclusion:** This study found that a deprescribing intervention was safe and effective in reducing the total medication burden at post-acute care discharge and 90 days after discharge.

Vasilevskis, E., et al. Deprescribing Medications among Older Adults from End of Hospitalization through Post-Acute Care: A Shed MEDS Randomized, Clinical Trial. *JAMA Intern Med.* 2023. doi:10.1001/jamainternmed.2022.6545.

### SERUM C3 COMPLEMENT LEVELS AND PROGNOSIS IN GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis. The complement pathway is part of the immune system, protecting the host from pathogens. This study examined the role of serum C3 and C4 levels as biomarkers of GBS.

Subjects were patients hospitalized between January, 2010 and October, 2021 with a diagnosis of GBS. Clinical outcomes were correlated with baseline serum C3, C4, as well as four existing biomarkers (GM1, albumin, immunoglobulin G, and neutrophil-lymphocyte ratio) and three clinical factors from the modified Erasmus GBS outcome score model. Clinical outcomes were determined with GBS Disability Scores and Medical Research Council Sum Scores (MRCSS) at admission, the nadir, and discharge.

Data were analyzed for 76 patients with a mean age of 55 years. Anti-ganglioside antibodies were detected in 23%. At the nadir, 62% could not walk unaided and 15%

experienced respiratory insufficiency. A negative relationship was observed between C3 levels and MRCSS at each time point. In addition, higher C3 was associated with greater functional disability at the nadir ( $p=0.014$ ), discharge, ( $p<0.001$ ), one month ( $p=0.002$ ), and three months ( $p<0.001$ ). No significant relationship was found between C4 and the outcome parameters. A multivariable regression analysis revealed that independent predictors of outcome at one- and three-month follow-up included older age, severe muscle weakness on admission, and higher baseline C3 levels.

**Conclusion:** This study of patients with acute Guillain Barre syndrome found that complement C3 at baseline was significantly related to clinical outcome.

Min, Y., et al. Serum C3 Complement Levels Predict Prognosis and Monitor Disease Activity in Guillain Barre Syndrome. *J Neurol Sc.* 2023, January; 444. doi: 10.1016/j.jns.2022.120512.

### PERIOPERATIVE NUTRITIONAL SUPPLEMENT AND WOUND HEALING

Among patients undergoing lumbar spine surgery, malnutrition has been found to range from five percent to 50%. This study investigated whether perioperative nutritional intervention could affect the risk of wound healing complications among patients undergoing elective lumbar spine surgery.

This prospective, randomized, controlled trial included 103 patients, 55 years of age or older, scheduled for lumbar spine surgery. On the day of surgery, the patients underwent serum laboratory workup, including albumin, pre-albumin and transferrin measures, to assess baseline nutritional status. Those randomized to an intervention group were provided a protein shake containing 30 grams of protein, 150 calories, and one gram of sugar, twice daily beginning on post-operative day zero, and continuing through the hospital stay, with a two-week supply given upon discharge. Follow-up after discharge occurred at two, four, six, and 12 weeks. The primary outcome variables included minor complications during hospitalization and wound healing complications within 90 days of surgery.

Data were analyzed for 103 patients with a mean age of 63.6 years. Malnutrition, defined as a pre-



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operative albumin of less than 3.5 g/dl, was found in 37 patients. At follow-up, wound healing complications were noted in 17.9% of the control group and 3.4% of the treatment group ( $p < 0.05$ ). Of the patients who were malnourished at baseline, those in the supplementation group had lower rates of minor complications during the index admission (0.0% versus 34.4%,  $p = 0.01$ ). Minor complications were noted in 23.1% of the controls and 2.1% of the treatment group ( $p = 0.03$ ).

**Conclusion:** This study of patients undergoing elective lumbar spine surgery found that a perioperative nutritional supplement could reduce minor complications during admission and wound complications within 90 days.

Saleh, H., et al. Perioperative Nutritional Supplementation Decreases Wound Healing Complications following Elective Lumbar Spine Surgery: A Randomized, Controlled Trial. *Spine* 2023, March 15; 48(6): 376-383.

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