

# REHAB IN REVIEW

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## LIGHT CIGARETTE SMOKING AND MORTALITY

From 1987 to 2020, the prevalence of smokers in Spain decreased from 38.1% to 22.1%. During that time the proportion of smokers consuming fewer than 10 cigarettes per day increased from 23% to 37%. This study explored the association between the number of cigarettes consumed per day and all-cause mortality.

This longitudinal, prospective study included individuals 15 years of age or older who participated in the 2011-2012 National Health Survey or the 2014 European Health Survey for Spain. The main variable was tobacco consumption, with individuals grouped as never-smokers, ex-smokers, non-daily smokers, and daily smokers. Data gathered included the sociodemographic covariates, lifestyle and health status, adherence to the Mediterranean diet, and self-reports of health.

Data were analyzed for 42,902 participants. Compared with never-smokers, the risk of mortality was higher for ex-smokers (Hazard Ratio (HR) 1.29), non-daily smokers (HR 1.30), smokers of one to two cigarettes per day (HR 2.23), and smokers of more than 30 cigarettes per day (HR 2.96).

**Conclusion:** This study found that light cigarette smoking, even non-daily smoking, was associated with an increased risk of mortality.

Galan, I., et al. Light Cigarette Smoking and All-Cause Mortality in Spain. A National, Population-Based, Cohort Study. *Ann Epidemiol.* 2023, February; 78: 9-12.

## TRANSCRANIAL DIRECT STIMULATION WITH CONSTRAINT-INDUCED THERAPY AFTER STROKE

Constraint-induced movement therapy (CIMT) has been found to accelerate the recovery of the upper extremity after a stroke. In addition,

transcranial direct current stimulation (tDCS) has been shown to accelerate the recovery of several symptoms of patients with a recent stroke. This study assessed whether the combination of these two interventions can improve motor recovery in patients with stroke.

This randomized, double-blind, clinical trial included adults with an acute ischemic stroke within 14 days of onset. The patients were randomized to receive CIMT(C) or CIMT combined with tDCS (C-DCS). The CIMT treatment involved the restriction of movement of the unaffected hand for six hours per day while training the affected upper extremity with two, one-hour sessions per day. The tDCS was applied during the first 20 minutes of one of the two upper extremity training sessions. The patients were assessed at baseline and follow-up with the Fugl Meyer Assessment-Upper Extremity (FMA-UE), the Functional Independence Measure (FIM) and the Wolf Motor Function Test (WMFT).

Data were analyzed for 56 patients with an average age of 65 years. At follow-up, scores on the FMA-UE, as well as the WMFT, were more improved in the C-DCS group than in the C group ( $p < 0.05$  for both comparisons). In addition, greater improvement was noted in the C-DCS group in scores of joint pain ( $p = 0.029$ ), and total FIM ( $p = 0.046$ ) scores.

**Conclusion:** This study of patients with acute ischemic stroke found that early transcranial direct current stimulation, combined with constraint-induced movement therapy, can improve motor function, pain, and disability more than constraint-induced therapy alone.

Garrido, M., et al. Early Transcranial Direct Current Stimulation with Modified Constraint-Induced Movement Therapy for Motor and Functional Upper Limb Recovery in Hospitalized Patients with Stroke: A Randomized, Multicenter, Double-

Blind, Clinical Trial. *Brain Stim.* 2023, January; 16(1): 40-47.

## DIRECT ORAL ANTICOAGULANTS FOR OCTOGENARIANS WITH VENOUS THROMBOEMBOLISM

Age is known to be an important risk factor for recurrent venous thromboembolism (VTE). Therefore, long-term anticoagulation is often recommended to prevent recurrent VTE and related death. Current guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKA) as first-line treatments for DVT, although these recommendations are based on studies with limited generalizability to older adults. This study assessed the effectiveness and safety of DOACs among octogenarians with VTE.

This retrospective cohort study obtained data from linked electronic databases concerning all patients with an incident inpatient or outpatient VTE. Data analysis was restricted to those  $\geq 80$  years of age. From these were identified all patients who initiated treatment with a DOAC or a VKA. The study's outcomes were recurrent VTE, major bleeding, and all-cause mortality at a median follow-up of 5.3-5.9 months.

Data were analyzed for 6,737 octogenarians who initiated treatment with DOACs ( $n = 3,778$ ) or VKAs ( $n = 2,959$ ). At follow-up, compared to VKAs, DOACs were associated with similar risks of recurrent VTEs, major bleeding, and all-cause mortality.

**Conclusion:** In this retrospective, multi-database, cohort study of nonagenarians diagnosed with a venous thromboembolism (VTE), those who received direct oral anticoagulant medications had risks of recurrent VTE, major bleeding, and all-cause mortality similar to those treated with a vitamin K antagonist.

Douros, A., et al. Effectiveness and Safety of Direct Oral Anticoagulants among Octogenarians with Venous Thromboembolism: An International,

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Multi-Database, Cohort Study. *Am J Med.* 2023, Jan;136(1):79-87.e7.

## **HIP STRENGTH, PHYSICAL FUNCTION, AND BALANCE IN OSTEOARTHRITIS OF THE KNEE**

Studies have demonstrated that people with osteoarthritis of the knee (KOA) use compensatory hip and trunk movement patterns during functional tests. This study assessed the association between hip muscle strength and dynamic balance in people with unilateral KOA.

The subjects were 47 adults with KOA and a mean age of 66.2 years. Strength was measured for hip flexion, abduction, adduction, internal rotation, external rotation, and extension. Participants performed the Star Excursion Balance Test (SEBT) and three physical function measures including the 40m fast-paced walk test(40mFPWT), the 30-s chair-stand test (30sCST), and the stair-climb test.

After adjusting for gender and age, measures of knee extension, hip flexion, hip abduction, hip external rotation, and hip extension strength were found to be associated with the results of the 40mFPWT and the stair-climb. The association with the greatest magnitude for the 40mFPWT was strength in knee extension ( $p < 0.001$ ), followed by hip extension ( $p < 0.001$ ). For the stair climb test, knee extension strength had the greatest magnitude ( $p < 0.001$ ), followed by hip external rotation and extension strength ( $p < 0.001$ ).

**Conclusion:** This study found that hip strength is associated with measures of physical function and dynamic balance in people with unilateral osteoarthritis of the knee.

Hislup, A., et al. The Association between Hip Strength, Physical Function and Dynamic Balance in People with Unilateral Knee Osteoarthritis: A Cross-Sectional Study. *Musculoskel Sci Pract.* 2023; 63: 102696.

## **EXTENDED KNEE CONTROL PROGRAM AND HAMSTRING KNEE AND ANKLE INJURY**

Some injury prevention exercise programs, such as the Knee Control Program (KCP) have been shown to reduce the rate of lower extremity injuries. However, athletic coaches often modify the KCP, potentially limiting its effectiveness. To improve the utility of the KCP an extended

version (KCP-Ex) was created, which included more exercise variations. This study was designed to assess the efficacy of the KCP-Ex for preventing injuries to the lower extremities.

The subjects were females, 14 years of age or older, participating in amateur football teams in Sweden. The teams were cluster randomized to use the KCP-Ex program, the Adductor Strength Program (ASP), or a self-selected prevention program (SS). The primary outcome variable was the injury incidence rate (IR), expressed as injuries/1,000 hours of participation, of the hamstring, knee, ankle, or groin. The secondary outcome variable was the IR for any injury, irrespective of location.

Data were collected from 17 teams with a total of 502 players. The IR was 7.72/1,000 hours for the KCP-Ex group, 9.36/1,000 hours for the ASP group, and 10.89/1,000 hours for the SS group. The differences reached significance only for the KCP-Ex versus SS comparison ( $p=0.36$ ). For all the physical complaints, the IRs were 17.15 for the KCP-Ex group, 23.20 for the ASP group, and 24.14 for the self-selected group. The differences were significant for the KCP-Ex group versus the ASP group ( $p=0.012$ ), as well as for the KCP-Ex group as compared to the SS group ( $p=0.02$ ).

**Conclusion:** This study of adolescent soccer players found that an injury prevention program emphasizing knee extension was superior to that relying on adductor strengthening for preventing lower extremity injuries.

Lindholm, H., et al. Extended Knee Control Program Lowers Weekly Hamstring, Knee and Ankle Injury Prevalence Compared with an Abductor Strength Program or Self-Selected Injury Prevention Exercises in Adolescent and Adult Amateur Football Players: A Two-Arm, Cluster-Randomised Trial with an Additional Comparison Arm. *Br J Sports Med.* 2023, January; 57: 83-90.

## **LYMPHEDEMA AND TOTAL HIP ARTHROPLASTY**

Lymphedema is thought to be a risk factor for postoperative complications, although few data clarify this risk. This study assessed the risk of infection-related complications following total hip arthroplasty (THA).

The joint registry of the author's institution was queried to identify all

adult patients who underwent primary THA between 1998 and 2016. These patients were followed retrospectively by cross-referencing the electronic medical record to identify those diagnosed with lymphedema prior to surgery. The matched control group had no diagnosis of lymphedema. The primary outcome measure was revision THA and surgery for any reason.

During the period of review, 20,930 patients underwent primary THA. Of these, 83 had ipsilateral lymphedema at the time of the surgery. Compared with controls (n=498), patients with lymphedema had an increased risk of reoperation (odds ratio (OR) 3.16), revision THA (OR 2.83), and infection (OR 4.48). Revision THA occurred in five patients (6%) with lymphedema (three related to infection) and 12 patients without lymphedema. Those with lymphedema had a five-year, infection-free survival of 90.3%, which was less than patients without lymphedema, at 97.7% (p<0.01).

**Conclusion:** This retrospective study of patients undergoing total hip arthroplasty found that the diagnosis of lymphedema prior to surgery is associated with an increase in the risk of reoperation and infection.

Rainer, W., et al. Lymphedema Is a Significant Risk Factor for Failure after Primary Total Hip Arthroplasty. *J Bone Joint Surg (Am)*. 2022, January 5; 104(1): 55-61.

### LUMBOSACRAL ORTHOSES AFTER DISCECTOMY

Lumbar disc herniation is commonly treated with surgical discectomy. Many protocols suggest the use of a lumbosacral orthosis for post-operative pain management. However, no clear evidence has supported the efficacy of this use of orthotics. This study investigated the benefits of postoperative orthoses in patients with lumbar disc herniation undergoing single-level discectomy.

This prospective cohort included 99 adults scheduled for single-level microscopic discectomy. Those patients were randomly assigned to either receive orthoses or not. The groups were compared by the rate of recurrence of disc herniation, as well as scores on the Japanese Orthopaedic Association for lumbar spine (L-JOA score) at two-week and one-year follow-ups. Pain in the lower extremities and low back were measured with the visual analog scale (VAS) and the Oswestry

Disability Index (ODI) at six-month and one-year follow-ups.

At one-year follow-up, 42 patients in the orthoses group in 39 in the control group remained in the study. During the first postoperative month, recurrence of disc herniation was noted in 7.1% of the orthoses group and in 15.4% of the control group (p=0.92). The length of hospital stays were 6.4 days for the orthoses group and 6.3 days for the control group. At one year, a repeat surgery was performed for two patients in each group. While not reaching significance, the six- and 12-month VAS pain scores for back and leg pain were higher in the control group.

**Conclusion:** This prospective study of patients undergoing single-level lumbar surgical discectomy suggests that wearing a lumbosacral orthosis may reduce the risk of surgical recurrence.

Sakaki, K., et al. Effectiveness of Lumbosacral Orthosis after Discectomy for Lumbar Disk Herniation: A Prospective, Comparative Study. *Spine*. 2023, January; 48(1): 15-20.

### SEAT BELT LAWS, AND SEAT BELT USE AMONG HIGH SCHOOL STUDENTS IN THE UNITED STATES

Motor vehicle crashes (MVCs) are the leading cause of death among adolescents in the United States (U.S.). This study assessed the association between seat belt legislation and the prevalence of seat belt use in high school students.

The Youth Risk Behavior Survey (YRBS) is a biannual, school-based, self-report survey conducted by the Centers for Disease Control and Prevention (CDC). Data from the YRBS were reviewed for seat belt use among high school students under 18 years of age. Responses were recorded as always (A) or not always (N-A) wearing a seat belt while in a car. Covariates were demographic characteristics, graduated driver licensing (GDL) laws, and enforcement. Primary enforcement was defined as allowing the police to issue a citation when a seat belt violation was observed. Secondary enforcement was defined as enforcement that could only occur if the vehicle was stopped by the police for other reasons.

Data obtained in 2019 included 81,929 students in 36 states. Among those subjects, 56% always wore a seat belt. This finding varied by state

from 40.8% in Louisiana to 68.5% in Maine. Those living in states with primary enforcement laws were five percent more likely to always wear a seat belt than those living in states with secondary enforcement laws.

**Conclusion:** This study of high school students in the U.S., all under 18 years of age, found that only 56% always wore a seat belt, with the likelihood greater in states with primary enforcement laws.

Pan, Y., et al. Seat Belt Laws and Prevalence of Use among High School Students in the United States. *Ann Epidemiol*. In Press. doi: <https://doi.org/10.1016/j.annepidem.2022.12.011>.

### HEALTHCARE EXPENDITURE IN PRIMARY ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Anterior cruciate ligament (ACL) reconstruction is among the highest-volume orthopedic procedures in the United States. This study was designed to describe and quantify the drivers of the costs of ACL repair, using a large, national database of privately insured patients.

Data were harvested from the MarketScan Commercial Claims and Encounters database, which includes over 32 billion service records for active employees, early retirees, and dependents insured by employer-sponsored plans. The database was searched for patients who had a Current Procedural Terminology (CPT) code of 29888 (arthroscopically aided anterior cruciate ligament repair/augmentation or reconstruction) between April 2013 and June 2017. The immediate procedure reimbursement included costs during a three-day window surrounding the procedure. Total health care utilization (THU) included costs incurred 90 days preoperatively to 100 days postoperatively.

Data were reviewed from the records of 34,862 patients. Of these, 59.9% underwent repair at an outpatient hospital (OH) and 40.1% at an ambulatory surgery center (ASC). The median THU for the ACLR was \$17,363. The three variables that most affected the immediate procedure reimbursement were the surgical setting of an OH (54.8% (\$6,599) increase over an ASC), an out-of-network provider (53.3% (\$6,418) increase over an in-network provider), and the procedure type of ACLR + meniscal repair + meniscectomy (29.3% (\$3528) increase over ACLR alone).

**Conclusion:** This study of patients undergoing anterior cruciate ligament reconstruction found that the cost of the procedure was significantly greater when performed in an outpatient hospital setting, using an out-of-network surgeon.

Tia, J., et al. Ambulatory Surgery Centers Significantly Decrease Total Health Care Expenditures in Primary Anterior Cruciate Ligament Reconstruction. *Am J Sports Med.* 2023, January; 51(1): 97-106.

### OPIOIDS, PAIN INTERVENTIONS, AND TOTAL COST OF SPINAL CORD STIMULATORS

Spinal cord stimulators (SCS) are neuromodulation devices implanted in the epidural space with the goal of treating chronic pain that fails to respond to conventional treatment. This study compared the long-term risk-benefit and cost-effectiveness of SCSs with conventional medical management (CMM).

This retrospective study used deidentified administrative claims data from U.S. commercial and Medicare Advantage enrollees treated for chronic pain. Adult patients who received a permanent SCS were compared to those treated with CMM only. The index date was the date of SCS insertion, with this date randomly chosen for the CMM group. The primary outcome variables were chronic opioid use, epidural injection or facet injection, occurring within 24 months.

Data were analyzed for 1,260 patients in the SCS group and 6,300 in the CMM group. At 12 months, the SCS group filled a higher number of opioid prescriptions and were more likely to have chronic opioid use (adjusted odds ratio (aOR) 1.14) than those treated with CMM. Treatment with SCS was associated with lower odds of epidural or facet corticosteroid injections (aOR 0.44) radiofrequency ablation (aOR 0.57), and spine surgery (aOR 0.44). The cost of care of was \$39,000 higher in the SCS group than in the CMM group.

**Conclusion:** This retrospective study of patients with chronic back pain found that spinal cord stimulator placement was not associated with a reduction in opioid use.

Dhruva, S., et al. Long-Term Outcomes in Use of Opioids, Non-Pharmacological Pain Interventions, and Total Cost of Spinal Cord Stimulators Compared with

Conventional Medical Therapy for Chronic Pain. *JAMA Neurol.* 2023, January. 80(1): 18-29.

### OCULAR MICROCIRCULATION AFTER CHOLESTEROL APHERESIS

Studies have demonstrated a close relationship between ocular microcirculation and the risk of cerebrovascular and cardiovascular events. This study reviewed the ocular microcirculation before and after lipoprotein apheresis in patients with inherited hypercholesterolemia.

The sample included 22 patients with inherited hypercholesterolemia, scheduled for lipoprotein apheresis. On the day of the study, the subjects underwent an eye exam, including laser speckle flowgraphy (LSFG) to measure optic disc blood flow. The eyes of the subjects were divided into two groups based upon pre-apheresis microcirculatory parameters (group one: lower microcirculatory parameters, group two: higher microcirculatory parameters). Plasma lipid levels were measured before and after apheresis.

After lipoprotein apheresis, significant decreases were found in plasma lipids in both groups, including total cholesterol ( $p < 0.001$ ), LDL cholesterol ( $p < 0.001$ ), triglycerides ( $p < 0.001$ ), and HDL cholesterol ( $p < 0.001$ ). However, microcirculatory parameters improved in group one but not group two.

**Conclusion:** This study of patients with inherited hypercholesterolemia demonstrates that optic disc blood flow, measured with laser spectography, could assess vascular improvement after lipoprotein apheresis.

Sampietro, T., et al. Acute Increase in Ocular Microcirculation Blood Flow upon Cholesterol Removal. The Eyes Are the Window of the Heart. *Am J Med.* 2023, January; 136 (1): 108-114.

### PREDICTING AWAKENING FROM COMA AFTER CARDIAC ARREST

Recent advances in the field of machine learning have given rise to powerful tools for modeling brain signals. Convolutional neural networks (CNNs) have been suggested as promising for extracting the complex features of EEG data. This study explored whether CNNs would be able to extract patterns of EEG responses to auditory

stimulation that relate to a patient's chances of awakening from a coma and survival at three months.

Data were recorded from a cohort of 145 comatose patients following a cardiac arrest. On the first day of the coma, bedside EEG data were collected, with CNNs used to model single-trial EEG responses to auditory stimuli. These responses were compared between those who did and did not awake from a coma as well as those who did and did not survive. Outcomes of survivors were assessed with the Cerebral Performance Category (CPC). The patients received scores on the CPC based on their level of recovery, with one indicating a full recovery, two, a return of consciousness with moderate disability, three, a return of consciousness with severe disability, four, a coma or persistent vegetative state and five for death.

Of the 134 patients analyzed, 59% survived, and 41% survived with a poor outcome (CPC four-five). The use of the CNNs resulted in a positive predictive power for awakening of 0.83 and for predicting outcome of 0.69.

**Conclusion:** This study of patients in a coma after a cardiac arrest found that EEG responses to auditory stimulation, evaluated with deep learning, could assist in predicting the chances of a patient's awakening from the coma.

Aellen, F., et al. Auditory Stimulation and Deep Learning Predict Awakening from Coma after Cardiac Arrest. *Brain.* 2023 Jan 13: awac340. Doi: 10.1093/brain/awac340. Online ahead of print.

### THERAPY FOR VISUAL SNOW SYNDROME

Visual snow syndrome (VNS) is a neurological condition characterized by constant flashing dots or static throughout the visual field. This study assessed the efficacy of neuro-optometric rehabilitation (NORT) for the treatment of VNS.

Data were completed for 21 patients recruited from the Visual Snow Initiative database. The patients received an in-office examination with objective measurement of eye movements using an electronic eye tracking system. The NORT eye-tracking consisted of 12, 60-minute one-on-one sessions of three to five exercises, with home assignments performed five days per week for 12 weeks. The primary outcome

measure was the NEI Visual Function Questionnaire 25-2000 edition (NEI-VFQ-25) composite score of self-reported visual health and quality of life.

Overall, the mean score of the participants' QOL improved significantly after six and 12 weeks of treatment for composite, distance, and near vision scores. At six weeks, NEI-VFQ-25 scores were significantly improved ( $p=0.0007$ ). This trend of improvement continued into the 12th week of treatment ( $p=0.0002$ ). No significant change was seen in general health, ocular pain, color vision, or peripheral vision. The results for general vision did not show improvement at six weeks but did show improvement at 12 weeks.

**Conclusion:** This study of patients with visual snow syndrome found that neuro-optometric rehabilitation therapy may be effective in improving quality of life.

Tsang, T., et al. The Efficacy of Neuro Optometric Visual Rehabilitation Therapy in Patients with Visual Snow Syndrome. *Frontiers Neurol.* 2022, Dec 5;13:999336. doi: 10.3389/fneur.2022.999336.

### DEPRESSIVE SYMPTOMS AND POSTCONCUSSIVE SYMPTOMS

While the rate of recovery varies, the vast majority of patients with a concussion or mild traumatic brain injury recover within two weeks following the injury. A significant minority will experience symptoms for months or years following injury, often referred to as persistent post-concussion symptoms (PPCSs). As some data have shown an association between PPCSs and depression, this meta-analysis was designed to better understand the association between depressive symptoms and PPCSs.

A literature review was completed for studies involving participants diagnosed with a concussion, with a Glasgow Coma Scale score between 13 and 15, loss of consciousness for 30 minutes or less, and/or post-traumatic amnesia of less than 24 hours duration. Eligible subjects had symptoms of concussion lasting for more than four weeks.

Eighteen studies, involving 9,101 participants, met the inclusion criteria and were included in the systematic review and meta-analysis. A random effects meta-analysis identified a positive association between PPCSs

and post-injury depressive symptoms with an odds ratio of 4.56 ( $p<0.001$ ).

**Conclusion:** This systematic review and meta-analysis revealed a significant association between persistent post-concussive syndrome and depressive symptoms.

Lambert, M., et al. Depressive Symptoms in Individuals with Persistent Post Concussion Symptoms: A Systematic Review and Meta-Analysis. *JAMA Network Open.* 2022; 5(12): e2248453. doi:10.1001/jamanetworkopen.2022.48453.

### TRANSCUTANEOUS OR REGULAR VAGUS NERVE STIMULATION FOR MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is the pathological state of pre-dementia with the manifestation of the progressive decline of memory or other cognitive functions. This study assessed the efficacy of transcranial auricular vagus nerve stimulation (taVNS) for the treatment of MCI.

The subjects were 55 to 75 years of age with a clinical diagnosis of MCI. The participants were randomized to receive either taVNS or shamVNS. In the taVNS group, stimulation was applied to two acupoints, including heart (concha, CO<sub>15</sub>) and kidney (CO<sub>10</sub>), which are in the distribution of vagus nerve. In the sham group, two other auricular acupoints were stimulated, including the elbow (scaphoid fossa, SF<sub>3</sub>) and shoulder (SF<sub>4,5</sub>), which are outside of the distribution of the vagus nerve. The subjects underwent two, 30-minute sessions per day, five days per week for 24 weeks. The primary outcome measure was the Montreal Cognitive Assessment- Basic (MOCA-B).

Sixty patients were included in this study, with no significant difference in baseline scores between the two groups. At 24 weeks, compared to the shamVNS group, the taVNS group demonstrated significantly better scores on the MoCA-B ( $p=0.033$ ). Of the secondary outcomes, compared to baseline, greater improvement was found in the taVNS group on the Auditory Verbal Learning Test-HuaShan version for short-term memory ( $p<0.05$ ) and long-term memory ( $p<0.01$ ).

**Conclusion:** This study of patients with mild cognitive impairment found that transcutaneous auricular vagus nerve stimulation improved cognitive performance.

Wang, L., et al. The Efficacy and Safety of Transcutaneous Auricular Vagus Nerve Stimulation in Patients with Mild Cognitive Impairment: A Double-Blinded, Randomized, Clinical Trial. *Brain Stim.* 2022, Nov-Dec; 15 (6): 1405-1414.

### NEUROMUSCULAR COMPLICATIONS OF THE LEG AFTER LUNG TRANSPLANTATION

Studies have shown that, after lung transplantation (LT), neurologic complications are common, although most studies have focused on the central nervous system. This study assessed the occurrence of peripheral neuropathy of the lower extremities after LT.

This retrospective analysis used data gathered from patients who underwent LT between March 2013 and June 2020. The cause of weakness was confirmed by electromyographic diagnostic testing and functional status with the Modified Ranking Scale (mRS). Data were gathered for 201 patients, of whom 156 had no postoperative leg weakness, 16 (8%), developed asymmetric weakness, and 29 (14.4%) developed symmetrical weakness.

Multivariate analysis revealed that the use of preoperative extracorporeal membrane oxygenation (ECMO) was independently associated with asymmetric weakness (Odds Ratio (OR) 3.590). Symmetric leg weakness was associated with age at LT (OR 1.062), diabetes mellitus (OR 2.873), myositis (OR 13.250), postoperative continuous renal replacement therapy (OR 4.858), and duration of stay in the intensive care unit (OR 1.052).

**Conclusion:** This study of patients undergoing lung transplants found that more than 20% develop leg weakness after surgery.

Cho, S., et al. Risk Factors for Neuromuscular Complications in Lower Limbs after Lung Transplantation. *Front Neurol.* 2023, January. doi.org/10.3389/fneur.2022.1066104.

### VIRAL EXPOSURE AND NEURODEGENERATIVE DISEASE

Research has demonstrated an increased risk of contracting multiple sclerosis among those previously infected with the Epstein-Barr virus. Other studies have suggested an

association between exposure to various viruses and the onset of neurodegenerative disease (NDD). This study was designed to better understand the relationship between viral exposure and the risk of developing an NDD.

Data were mined from FinnGen, a nationwide Finnish biobank with genotyping data available for more than 300,000 individuals. Data were also obtained from the United Kingdom biobank (UKB) for replication. In the first portion of the study, the data were reviewed for viral exposure preceding NDD onset. From this review were identified 45 significant NDD/virus associations in the FinnGen, of which 22 were replicated in the UKB.

The highest hazard ratio (HR) was seen for the association between viral encephalitis and Alzheimer's disease (AD), with an HR of 22.06 in the replication phase. The majority of the replicated associations included viruses commonly considered to be neurotrophic. Influenza and pneumonia were significantly associated with five of the six NDDs (AD, ALS, dementia, PD, and VAS). Reviewing all FinnGen virus-NDD pairings for which data was available, 17 pairs remained significant at five to 15 years between exposure and diagnosis.

**Conclusion:** This study demonstrates an association between viral infections and subsequent neurodegenerative diseases.

Levine, K., et al. Viral Exposure and Neurodegenerative Disease Risk across National Biobanks. *Neuron*. 2023, Jan 11;S0896-6273(22)01147-3. doi: 10.1016/j.neuron.2022.12.029. Epub ahead of print. PMID: 36669485.

### NEUROINFLAMMATORY PATHWAYS AND PAIN WITH CHEMOTHERAPY

Approximately 70% of patients experience moderate to severe pain during chemotherapy. As previous studies have demonstrated that perturbations in neuroinflammatory pathways are associated with chemotherapy-induced peripheral neuropathy, this study screened for perturbations in neuroinflammatory pathways.

Subjects were adults with a diagnosis of cancer who had received chemotherapy within the preceding four weeks. Of the 1,343 patients who consented, 717 patients provided a

blood sample to assess the neuroinflammatory pathways. Data were also collected concerning demographics, clinical characteristics, and pain, using the Brief Pain Inventory. Those reporting the occurrence of pain for one or fewer of the six assessments were placed in the "none" group (n=371, 28.4%) and were compared to those who reported severe pain.

Compared to the none group (n=86), those in the severe pain group (n=111) were more likely to have perturbations in the neuroinflammatory pathways, including cytokine-cytokine receptor interaction, chemokine signaling pathway, phagosome, complement, coagulation cascades, and the JAK-STAT signaling pathway. In addition, the severe group was more likely to have perturbed neurotransmitter pathways, including retrograde endocannabinoid signaling, glutamatergic synapses, and GABAergic synapses.

**Conclusion:** This study demonstrates that perturbations in several neuroinflammatory pathways are associated with severe pain in patients with cancer who are receiving chemotherapy.

Shin, J., et al. Perturbations in Neuroinflammatory Pathways Are Associated with a Worst Pain Profile in Oncology Patients Receiving Chemotherapy. *J Pain*. 2023, Jan 24 (1): 84-97.

### AMNIOTIC MEMBRANE WRAPPING OF THE ULNAR NERVE DURING CUBITAL TUNNEL SURGERY

Cubital tunnel syndrome is the second most common compressive neuropathy of the upper extremity. Among those who undergo surgical correction, recurrence can occur, with some cases attributable to perineural fibrosis and scarring, resulting in compression of the nerve. As amnion has been shown to prevent scar tissue formation, this study assessed the effect of human amniotic membrane (HAM) wrapping in patients undergoing cubital tunnel procedures.

Subjects were 78 patients undergoing primary cubital tunnel surgery who underwent follow-up at over 90 days. Of those, 21 patients (26.9%) underwent HAM wrapping at the time of the index procedure, while 57 (73.1%) did not, and served as a control (CON) group.

At an average follow-up interval of 447.4 days, symptoms were assessed, with those of the HAM group compared to the CON group. A recurrence of symptoms was found in 19.3% of the CON group and zero percent of the HAM group (p=0.03). Multivariate regression analysis revealed that the CON group was 24.4 times more likely than the HAM group to develop symptom recurrence.

**Conclusion:** This retrospective study of patients undergoing primary cubital tunnel surgery found that the recurrence of symptoms was reduced among those whose nerves were wrapped with human amniotic membrane during the surgical procedure.

Mirzayan, R., et al. Human Amniotic Membrane Wrappings of the Ulnar Nerve during Cubital Tunnel Surgery Reduces Recurrence of Symptoms. *Arch Bone Joint Surg*. 2022, Nov; 10(11): 969-975.

### CHLOROTHIAZIDE VERSUS HYDROCHLOROTHIAZIDE FOR HYPERTENSION

Thiazide diuretics are first-line antihypertensive agents that lower blood pressure and prevent adverse cardiovascular outcomes. Despite guidelines that recommend chlorthalidone as the preferred agent, a 2020 report of Medicare expenditures found that 1.5 million persons received chlorthalidone and 11.5 million received hydrochlorothiazide (HCTZ). The Diuretic Comparison Project compared the efficacy of these two medicines.

This study included patients in the Department of Veterans Affairs health system, 65 years of age or older, with a systolic blood pressure of >120 mm Hg and an active prescription for HCTZ of 25 or 50 mg per day. The subjects were randomized to continue HCTZ or to switch to chlorthalidone at a daily dose of 12.5 or 25 mg. The primary outcome variable was the first occurrence of a composite outcome including a nonfatal cardiovascular disease event or a non-cancer-related death. Nonfatal cardiovascular disease events included nonfatal myocardial infarction, stroke, hospitalization for heart failure, or urgent coronary revascularization for unstable angina.

A total of 13,523 underwent randomization. At a median follow-up of 2.4 years, a primary composite

outcome event occurred in 10.4% of the chlorothiazide group and 10% of the HCTZ group ( $p=0.45$ ). There was no significant difference between the two groups in the occurrence of myocardial infarction, stroke, hospitalization for heart failure, revascularization for unstable angina, or non-cancer-related death.

**Conclusion:** This large study of patients in the Veterans Affairs health system found that those whose hypertension was treated with chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or non-cancer-related deaths than those treated with hydrochlorothiazide.

Ishani, A., et al. Chlorthalidone versus Hydrochlorothiazide for Hypertension-Cardiovascular Events. *N Engl J Med.* 2022, December 29; 387(26): 2401-2410.

### SELF-TREATMENT FOR RECURRENT BENIGN PAROXYSMAL VERTIGO

Benign paroxysmal positional vertigo (BPPV) is thought to be caused by dislodged otoconia that enter the semicircular canals. After successful treatment, BPPV has an annual recurrence rate of 15% to 18%. This study was designed to determine the therapeutic efficacy of self-administration of the canalith repositioning maneuver (CRM).

Subjects were adults with a diagnosis of BPPV, all of whom had previously and successfully been treated with CRM. Those participants were randomized to a control group or a treatment group, with the latter instructed to access the *Stop! BPPV* website when they experienced an episode of BPPV. This website prompted them to complete a questionnaire and then provided them with a video clip for the self-application of the CRM, appropriate for their subtype of BPPV. Patients in a control group received a video clip for self-administration of CRM according to the type of BPPV that had been diagnosed on enrollment. The primary endpoint was the resolution of positional vertigo after the application of the CRM.

Data was completed for 292 in the treatment group and 293 in the control group, with a mean recurrence interval of 179.8 days. In an intention-to-treat analysis, at follow-up, 72.4% of the treatment group and 42.9% of the control group

reported a resolution of their vertigo symptoms ( $p<0.001$ ).

**Conclusion:** This study of patients with benign paroxysmal vertigo found that a questionnaire-based diagnosis and self-administration of the canalith repositioning maneuver could effectively treat recurrent symptoms.

Kim, H., et al. Effect of Self-Treatment of Recurrent Benign Paroxysmal Positional Vertigo: A Randomized, Clinical Trial. *JAMA Neurol.* 2023, January 17. doi: 10.1001/jamaneurol.2022.4944.

### ASSOCIATION BETWEEN PCSK9 AND SUBCLINICAL CEREBRAL VASCULAR DISEASE

Three classes of low-density lipoprotein cholesterol-lowering medications have been found to beneficially affect cardiovascular disease. These include statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Recent studies have found that PCSK9 inhibitors may have multiple additional functions involving atherosclerotic progression. This study evaluated the relationship between serum levels of PCSK9 and subclinical cerebrovascular disease (CVD).

The Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) is a cross-sectional and prospective cohort study involving 2,379 Japanese men, 40 to 79 years of age. A baseline survey was conducted from 2006 to 2008 with a follow-up from 2010 to 2014. A brain MRI was obtained from 2012 to 2015. In 2018 serum PCSK9 was measured from previously frozen blood samples. Subjects were excluded from the analysis who were taking lipid-lowering medications or had a history of cardiovascular disease (CVD). The data collected included sociodemographic and behavioral data, physical exams, and laboratory testing including diabetic and lipid profiles. The group was divided into two groups based on their serum PCSK9 levels, as lower or higher than the population median of lower or 240 ng/mL.

Data were analyzed for 526 men with a median baseline age of 69 years. The MRI found cerebral microbleed (CMB) in 13.5%, deep and subcortical white matter hyperintensities; (DSWMH) in 21.9%, intracranial artery stenosis (ICAS) in 25.9%, and lacunar infarction (LI) in

18.1%. Serum PCSK9 levels were associated with the prevalence of ICAS in both univariable (Odds Ratio (OR)1.18) and multivariable analysis (OR 1.16). In addition in the univariable analysis, PCSK9 was associated with LI ( $p<0.05$ ) There were no significant associations between PCSK9 levels and the presence of LIs DSWMHs, PVHs or CMBs.

**Conclusion:** This Japanese study of community-dwelling men found that serum levels of proprotein convertase subtilisin/kexin type 9 were significantly associated with the prevalence of lacunar infarcts and of intracranial artery stenosis.

Kunimura, A., et al. Association Between Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) And Subclinical Cerebral Vascular Disease In The Community. *European J Neurol.* 2023, Feb. doi: 10.1111/ene.15723.

### SEMAGLUTIDE FOR ADOLESCENTS WITH OBESITY

According to the World Obesity Federation, by the year 2030, 250 million children and adolescents will be living with obesity. For young people, management guidelines recommend multimodal lifestyle modification. However, studies have shown that the results of these modifications are generally modest, with long-term maintenance rarely achieved. Some have considered pharmacological intervention if lifestyle intervention alone has been ineffective. The United States Food and Drug Administration has approved once-daily liraglutide (3.0 mg), orlistat (120 mg), and phentermine-topiramate (7.5 mg of phentermine with 46 mg of topiramate or 15 mg of phentermine with 92 mg of topiramate) for adolescents 12 years of age and older. The Semaglutide Treatment Effect in People with Obesity (STEP) Teens trial was designed to assess the efficacy and safety of once-weekly, subcutaneous injection of semaglutide for adolescents with obesity.

This double-blind, parallel-group, randomized, placebo-controlled, phase three clinical trial included adolescents 12 to 18 years of age with BMI at the 95th percentile or above, all of whom had experienced at least one unsuccessful dietary weight-loss effort. The subjects were randomized to an intervention (I)

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group or a placebo (P) group. All entered a 12-week lifestyle intervention program. Those in the I group received subcutaneous semaglutide 2.4mg/week while the P group received a matching placebo for 68 weeks.

Data were collected for 132 participants in the I group and 64 in the P group. The mean percentage changes in BMI from baseline to week 68 were -16.1% in the I group and -0.6% in the P group ( $p < 0.001$ ). A loss of at least five percent of their body weight was achieved by 73% of those in the semaglutide group and 18% of the placebo group ( $p < 0.001$ ). Adverse events were reported in 79% of the I group and 82% of the P group.

**Conclusion:** This phase study of adolescents with obesity found that, combined with lifestyle intervention, once-weekly subcutaneous semaglutide, 2.4mg, could significantly reduce body mass index.

Weghuber, D., et al. Once Weekly Semaglutide in Adolescents with Obesity. *N Engl J Med.* 2022, December 15; 387(24): 2245-2257.

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