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DNA METHYLATION AGE PREDICTS MORTALITY AFTER HIP FRACTURE

The DNA methylation clock involves the assessment of genomic damage through the analysis of DNA methylation. This process is a putative model of biologic rather than chronological age. This study used bone-derived DNA to establish a predictive relationship between preoperative DNA methylation age and postoperative mortality.

The subjects were forty-seven patients, 65 years of age or older, treated for a hip fracture between 2020 and 2021. Blood and bone samples were collected, for methylation clock analysis. The difference between chronological age and methylation age was determined using bone derived DNA (delta bone) and blood derived DNA (delta blood). The mean follow-up duration was 12.4 months.

The mean chronologic age of the patients who survived for at least 12 months following surgery was 82.6 years. The mean DNA methylation age for these patients was 89.9 years using blood derived DNA (82.6-89.9=delta of 7.3years) and 90.5 years for bone derived DNA (82.6-90.5=delta of 7.9 years). However, looking at only those who died within 12 months, the mean chronological age was 89.9 years, while the mean blood derived methylation age was 107.9 and the mean bone derived methylation age was 109.3 years (p=0.026).

Conclusion: This study of patients presenting with a hip fracture found that those who died within one year of surgical repair had a methylation age 17 years greater than their chronological age.

Tarpada, S., et al. Blood and Bone Derived DNA Methylation Ages Predicts Mortality after Geriatric Hip Fracture. A Pilot Study. **J Bone Joint Surg**. 2024. doi: 10.2106/ JBJS.23.01468.

GAIT PERFORMANCE IN OLDER ADULTS ACROSS THE COGNITIVE SPECTRUM

As the global population ages, dementia and falls have become a major public health concern. Because studies have shown that gait impairment may serve as an early marker of cognitive decline, this study explored whether specific components of gait are best at distinguishing between cognitive groups.

The Gait and Alzheimer Interactions Tracking (GAIT) prospective study recruited 711 subjects with a mean age of 72 years. Eligible subjects were 60 years of age or older, community dwelling, and ambulatory, without visual impairment or depression, and obtained Mini-Mental State Examination scores of over 10. All underwent gait assessments, including measures of gait speed, coefficient of stride time (CoV STV), and coefficient of step length variability (CoV SLV). Dual task procedures during gait included counting backward from 50 and animal naming.

The subjects were 332 cognitively healthy individuals, 264 individuals with mild cognitive impairment (MCI), and 115 with dementia. Those with MCI performed more poorly than did the control group on all gait tests. Those with dementia had slower gait speeds and higher variability coefficients than did the other two groups. The greatest ability to discriminate between controls and those with cognitive impairment occurred with the dual task involving the naming of animals. Of the gait parameters used during this task, the coefficient of stride length variability was most effective in discriminating between MCI and dementia.

Conclusion: This study of patients 60 years of age or older found that the gait parameter that best discriminates between normal cognitive function, mild cognitive impairment, and dementia is a dual task involving the naming of animals.

Ali, P., et al. Gait Performance in Older Adults across the Cognitive Spectrum: Results from the GAIT Cohort. **J Am Geriatr Soc**.2024 Nov;72(11):3437-3447.

MATERNAL COVID-19 VACCINATION IN EARLY PREGNANCY AND CONGENITAL ANOMALIES

Physiological and immunological changes during pregnancy increase the risk of severe COVID-19 disease, compared with that of non-pregnant women. This study examined the association between an mRNA COVID-19 vaccine in the first trimester of pregnancy and major congenital anomalies in offspring.

This population based, retrospective, cohort study and sibling matched analysis included singleton live birth at over 20 weeks' gestation, with an expected birth date between October, 2021, and May, 2023. For a sibling matched analysis, the study included older siblings with the same mother who were not exposed to the COVID-19 vaccine in utero. Maternal newborn pairs were identified from the MOMBABY database of linked hospital delivery records of mothers and newborns from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). The primary exposure was an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) during the first trimester. Major congenital anomalies were identified from the International Statistical Classification of Diseases and Related Health Problems.

Data were reviewed from the records of 34,181 infants born to mothers who received a COVID-19 vaccine (vaccine group) and 34,951 who did not receive the vaccine before or during pregnancy (control group). Major congenital anomalies were present in 832 (24.3 per 1000 live births) infants in the vaccine group and 927 (26.5 per 1000 live births) infants in the control group. Comparisons within the same family revealed that major congenital

anomalies were present in 283 (21.3 per 1,000 live births) of those in the vaccine group and 343 (22.7 per 1,000 live births) in the older siblings not exposed to a vaccine, (adjusted prevalence ratio 0.91).

Conclusion: This large, population-based study found that an mRNA COVID-19 vaccination during the first trimester of pregnancy was not associated with an increase in major congenital abnormalities in the offspring.

Jorgensen, S., et al. Association between Maternal mRNA COVID-19 Vaccination in Early Pregnancy and Major Congenital Anomalies in Offspring: Population Based, Cohort Study, Sibling Matched Analysis. **BMJ Med.** 2024, Sep 16;3 (1):e000743**.**

OBESITY AND PRIMARY TOTAL KNEE ARTHROPLASTY

In the United States the prevalence of obesity has increased over time and is expected to affect 50% of adults by the year 2030. As this coincides with an increase in the aging of the population, a greater number of patients with obesity will be undergoing total knee arthroplasty (TKA). This study analyzed trends in the association between postoperative complications and body mass index (BMI) among those undergoing TKA.

Data were obtained from the total registry from a single institution from 1990 through 2019. Patients were classified by BMI as non-obese, (BMI<30 kg/m^2) Class-I and II obese (BMI, 30 to 39.9 kg/m^2), and Class-III obese (BMI, ≥40 kg/m^2). The mean age at the time of surgery was 69 years and the mean BMI was 33 kg/m^2. Complications requiring surgical intervention within two years of the index surgery were identified and compared by BMI categories.

Data were analyzed for 13,919 subjects, including 5,435 non-obese, 4,185 Class I, 2,446 Class II, and 1,853 class III obesity participants. Between 1990 and 2019, there was a 90% increase in the prevalence of Class II obesity and a 300% increase in class III obesity. The entire cohort of patients experienced a significant decrease in the two-year revision risk over the study period (p<0.001). A significant decrease was noted in the two-year risk of PJI for the entire group (p=0.017), as well as the non-obese group (p=0.005), but for none of the obese groups. The two-year risk of any aseptic revision decreased for the entire cohort (p=0.002), Class-I and II obese patients (p = 0.011), and Class-III obese patients (p = 0.023).

Conclusion: This study of patients undergoing knee replacement surgery over the past 30 years found decreasing risks of reoperation, revision, and PJI for the entire cohort, including the obese.

Uvodich, M., et al. Outcomes of Obese Patients Undergoing Primary Total Knee Arthroplasty: Trends Over 30 Years. **J Bone Joint Surg**. 2024, Nov 6; 106(21): 1963-1970.

EFFICACY OF RUNNING FOR CHRONIC LOW BACK PAIN

Studies have shown that running is correlated with lower rates of low back pain (LBP) and overall healthier spinal tissue. However, little is known about the efficacy of running in individuals with chronic LBP (C-LBP). This study assessed the effect of recreational running in people with C-LBP as a modality to improve function and reduce pain intensity.

This trial recruited 40 adults, 18 to 45 years of age, randomly assigned to either exercise training or waitlist control (1:1). The intervention group was placed in a 12-week, progressive, run-walk program, including three, 30-minute sessions per week. The sessions were administered virtually, with remote support from an exercise physiologist. The control group was placed on a waitlist, to perform the program at a later time. Both groups were assessed at baseline and at 12 weeks. Outcome measures included self-reported pain intensity, assessed on a 100-point visual analog scale (VAS), and disability, measured by the Oswestry Disability Index (ODI).

At 12-weeks, compared to the control group, the treatment group had greater improvement in the mean VAS pain intensity (p=0.003), current VAS pain intensity (p=0.003), and ODI disability scores (p=0.038). No serious adverse events were reported.

Conclusion: This study of adults with chronic low back pain found that 30 minutes of running, three times per week could improve pain and reduce disability.

Neason C., et al. Running Is Acceptable and Efficacious in Adults with Non-Specific Chronic Low Back Pain: The ASTEROID Randomized, Controlled Trial. **Br J Sports Med**. 2024. Published Online First: 07

October 2024. doi: 10.1136/bjsports-2024-108245.

ORAL METHOTREXATE FOR SYMPTOMATIC KNEE OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of chronic arthritis. While current treatment for OA includes non-steroidal anti-inflammatory drugs and intraarticular glucocorticoids, these have not proven to be effective for altering the pathologic mechanisms. This study assessed the treatment effects of methotrexate, a disease-modifying, antirheumatic drug, on pain in patients with advanced knee OA (KOA).

The subjects were adults with primary KOA, with pain on most days, with an average severity of 40 or higher on a 100 mm visual analog scale (VAS) of pain. Those participants were randomized to a placebo group or to a treatment group, to receive oral methotrexate, titrated to a maximum of 25 milligrams per week for 12 months. The primary outcome measure was pain, measured by the 10 point Numerical Rating Scale (NRS) at six months.

Data were analyzed for 155 adults with an average age of 60.9 years. From baseline to six months, mean knee pain decreased from 6.4 to 5.1 in the methotrexate group and from 6.8 to 6.2 in the placebo group (p= 0.03). The methotrexate group also experienced greater improvement at six months on the Western Ontario and McMaster Universities Osteoarthritis Index Stiffness (p=0.045) and Physical Function scales (p=0.008).

Conclusion: This study of patients with OA of the knee found that weekly methotrexate significantly improved pain and function, as measured at six months.

Kingsbury, S., et al. Pain Reduction with Oral Methotrexate in Knee Osteoarthritis: A Randomized, Placebo-Controlled, Clinical Trial. **Ann Intern Med.** 2024, Sep; 177(9): 1145-1156.

ZERLASIRAN FOR TARGETING LIPOPROTEINS

Lipoprotein(a), composed of apolipoprotein (a) and apolipoprotein B100 is increasingly recognized as a likely causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis. As the hepatic production of apolipoprotein(a) is a rate limiting step in the production of lipoprotein (a), this study examined the effect of zerlasiran, a small-interfering RNA that targets the hepatic synthesis of apolipoprotein(a).

The Assessment of Lipoprotein(a) Lowering in Cardiovascular Disease with SLN360 (ALPACAR-360) study is a phase II trial including adults 18 to 80 years of age with ASCVD. ASCVD was defined as a previous myocardial infarction, stroke, angiographically documented coronary artery disease, or peripheral arterial disease, or the presence of any coronary calcium, detected by computed tomography.

The subjects were randomized into one of five groups, including subcutaneous injections of placebo every 16 weeks for three doses, placebo every 24 weeks for two doses, zerlasiran, 450 mg every 24 weeks for two doses (Z-450-24), zerlasiran, 300 mg every 16 weeks for three doses (Z-300-16), or zerlasiran, 300 mg every 24 weeks for two doses (Z-300-24). The primary efficacy outcome was the time-averaged percent change in serum lipoprotein(a) concentration.

At week 36, compared to baseline, the mean percent reductions in lipoprotein(a) concentration were 94.5% in the Z-450-24 group, 96.4% in the Z-300-16 group, and 90% in the Z-300-24 group.

Conclusion: This study of patients with atherosclerotic cardiovascular disease found that treatment with Zerlasiran, a small interfering RNA, can reduce circulating levels of lipoprotein(a) by more than 90%.

Nissen, S., et al. Zerlasiran-A Small-Interfering RNA Targeting Lipoprotein (a): A Phase II, Randomized, Clinical Trial. **JAMA.** doi: 10.1001/ jama.2024.21957.

ORAL MUVALAPLIN FOR LOWERING OF LIPOPROTEIN

Previous studies have demonstrated that higher lipoprotein (a) levels are associated with an increased risk of cardiovascular disease and calcific aortic valve stenosis. Therapeutic options for patients with elevated lipoprotein(a) levels are currently limited. In addition, studies suggest that large reductions of 85 to 250 nmol/L may be needed to lower cardiovascular risk. Muvalaplin is the first agent developed to lower lipoprotein(a) levels by targeting the assembly process of the lipoprotein(a) particle. This study evaluated the effects of different doses of muvalaplin on serum lipoprotein(a) in adults with elevated lipoprotein(a) levels who were at high risk of cardiovascular events.

The sample comprised adults 40 years of age or older, all at high risk for cardiovascular events, and with serum lipoprotein(a) concentrations of 175 nmol/L or higher. Those participants were randomly assigned to receive a placebo or muvalaplin at 10mg/day, 60mg/day, or 240 mg/day for 12 weeks. The primary outcome measure was the percent change in lipoprotein from baseline to week 12 in each group. Secondary end points included the proportion of participants achieving a lipoprotein(a) concentration of less than 125 nmol/L at week 12, percentage changes in apolipoprotein B and hs-CRP concentrations.

After 12 weeks of treatment, reductions in lipoproteins were noted in all treatment groups but not in the placebo group. The percent change in lipoprotein(a) using the intact lipoprotein (a) assay were 0.5% with placebo and −47.4% for the 10mg group, −81.7% with for the 60mg group, and −85.8% for the 240mg group. The percentage changes in lipoprotein (a) when using the apolipoprotein(a) assay were −3.2% with placebo, -40.4% for the 10 mg group, -70.7% for the 60 mg group, and −68.9% for the 240 mg group. At week 12, placebo-corrected changes in apolipoprotein B levels were −8.9% at 10mg/day, −13.1% for the 60 mg group, and −16.1% for the 240 mg group.

Conclusion: This phase II study of patients with elevated serum lipoprotein(a) levels found that Muvalaplin, the first oral agent that inhibits lipoprotein(a) assembly, could dramatically reduce lipoprotein(a) levels, with no safety concerns noted.

Nicholls, S., et al. Oral Muvalaplin for Lowering of Lipoprotein(a): A Randomized Clinical Trial. **JAMA.** 2024, Nov 18; e2424017. doi: 10.1001/jama. 2024. 24017.

LOW DOSE TRIPLE SINGLE PILL FOR BLOOD PRESSURE

Recent guidelines for the initial treatment of HTN recommend using combinations of two blood pressure lowering drugs, and earlier use of

triple drug antihypertensive therapy, ideally as a single-pill combination (SPC). This study compared the efficacy of a new triple SPC (telmisartan, amlodipine, and indapamide (GMRx2)), to that of individual medications.

The subjects were 1,385 hypertensive adults randomly allocated to receive GMRx2, half dose, telmisartan 20 mg with indapamide 1·25 mg (TI), telmisartan 20 mg with amlodipine 2·5 mg (TA), or amlodipine 2·5 mg with indapamide 1·25 mg (AI). At six weeks the doses were doubled. The primary outcome variable was the difference between the treatment groups in the change of home-measured SBP from baseline to week 12.

After 12 weeks of treatment, the mean SBPs were 134/83 mmHg for the GMRx2 group and averaged 140/85 mmHg for dual combination groups. At 12 weeks, the mean home SBP was 126 mmHg in the GMRx2 group, which was lower than for each of the dual combinations: –2·5 versus TI, –5·4 versus TA and –4·4 versus AI (p<0·0001 for all).

Conclusion: This study of patients with mild to moderate HTN found that low dose, once per day, triple drug therapy (GMRx2) reduced BP more effectively than dual therapy.

Rodgers, A., et al. Efficacy and Safety of a Novel, Low-Dose, Triple, Single-Pill Combination of Telmisartan, Amlodipine and Indapamide, Compared with Dual Combinations for Treatment of Hypertension: A Randomised, Double-Blind, Active-Controlled, International Clinical Trial. **Lancet.** 2024**,** Oct 19; 404(10462) :1536-1546.

STATINS AND LONG-TERM OUTCOMES IN ACUTE HEART FAILURE

Hospital admissions provide an opportunity to identify and initiate evidence based medical therapies. While heart failure is not considered an indication for statin therapy, many patients with heart failure have independent indications for statin therapy. This study investigated the extent of statin therapy indications and the actual utilization of statin therapy before and at discharge among patients with acute decompensated heart failure (ADHF).

This single center, retrospective, cohort study utilized data from patients admitted with ADHF as one of their primary diagnoses. A statin indication was based on the criteria outlined in the European Society of Cardiology and the European Atherosclerosis Society Guidelines for the Management of Dyslipidemias. The patients were grouped according to their statin therapy status at discharge. The primary outcome variable was five-year mortality.

Data were analyzed for 5,978 patients with hospital discharge diagnoses of ADHF. Of these, 4,416 had an indication for statin therapy, while only 2,282 were admitted with statin therapy ongoing. At discharge 3,533 were provided a statin prescription. Compared to patients discharged with statin therapy, rates of 30-day mortality and one-year mortality were significantly higher (p<0.0001) among those without statins at discharge. Multivariable analysis found that statin therapy at discharge was a negative predictor of five-year all-cause mortality (p<0.001).

Conclusion: This study of patients hospitalized with acute heart failure found that those discharged with a statin prescription had lower 30-day, one-year, and five-year mortality.

Monayer, A., et al. Statin Therapy Impact on Long-Term Outcomes in Acute Heart Failure: Retrospective Analysis of Hospitalized Patients. **Internat J Cardio Heart Vasc.** 2024, May 20;53: 101431.

LEFT ATRIAL APPENDAGE OCCLUSION AFTER ISCHEMIC STROKE

For patients with atrial fibrillation (AF), oral anticoagulation therapy (OAT) has been shown to decrease the risk of ischemic stroke. However, the risk of recurrent stroke remains elevated even among those using OATs. As over 90% of thrombi in patients with AF form in the left atrial appendage (LAA), occlusion of the LAA (LAVO) has been trialed as a means to reduce the risk of ischemic stroke. This study evaluated the clinical benefits of LAVO for patients with thromboembolic events and/or persistent LA thrombus while taking an OAT.

Between 2010 and 2022, 433 patients with persistent LAA thrombi despite OAT underwent successful LAAO. These patients were matched with 422 controls who continued or switched to an alternate OAT. The primary outcome for this analysis was the time to first ischemic stroke.

The annualized rates of ischemic stroke were 2.8% per patient-year in the LAAO group and 8.9% in the OAT group (p<0.01). Intracranial hemorrhage occurred two times in the STR-OAC LAAO group and seven times in the OAT group (p=0.05).

Conclusion: This study of patients with atrial fibrillation who experienced an ischemic event despite oral anticoagulation therapy found that treatment with a left atrial appendage occlusion reduced the risk of recurrent stroke, compared to continued treatment with oral anticoagulants.

Maarse, M., et al. Left Atrial Appendage Occlusion versus Standard of Care after Ischemic Stroke, Despite Anticoagulation. **JAMA Neurol.** 2024;81(11):1150–1158. doi:10.1001/jamaneurol.2024.2882

NARINGENIN AND INFLAMMATORY HYPERALGESIA

Pain in the oral facial region is transmitted through small Aδ-fibers and unmyelinated C-fibers of trigeminal ganglion (TG) neurons to second order neurons in the spinal trigeminal nucleus caudalis (SpVc). Naringenin (NRG; 4′,5,7-thrihydrooxyflavanone) acts as a dietary phytochemical. and has been shown to inhibit primary sensory neurons of the dorsal root ganglion (DRG). This study explored the effect of NRG on inflammation-induced hyperexcitability in the spinal trigeminal nucleus caudalis (SpVc) related to hyperalgesia, comparing its impact with that of diclofenac (DIC).

The subjects were 30 adult, male Wistar rats, randomly placed into one of five groups of six per group. One group served as a control while the others were injected with complete Freund's adjuvant to provoke inflammation. One group received no medication and served as a control, with others provided with NRG (50 mg/kg), DIC (50 mg/kg) or a combination of DIC (25 mg/kg) + NRG (25 mg/kg). All were then tested for their mechanical threshold. Electrophysiological data were collected to record the activity of SpVc wide-dynamic range neurons in response to mechanical stimulation of the orofacial area under anesthesia.

The inflamed rats showed significantly lower mechanical thresholds. This threshold returned to normal levels two days post-administration of NRG, DIC, and half-dose DIC plus half-dose NRG (1/2

DIC + 1/2 NRG). In addition, the heightened average spontaneous activity of SpVc neurons was significantly reduced following NRG, DIC, and 1/2 DIC + 1/2 NRG administration.

Conclusion: This animal study of induced trigeminal neuralgia found that the administration of the phytochemical Naringenin was able to mitigate the inflammatory mechanical hyperalgesia related to the increased excitability of nociceptive spinal trigeminal nucleus caudalis.

Yajima, S., et al. Naringenin Suppresses the Hyperexcitability of Trigeminal Nociceptive Neurons Associated with Inflammatory Hyperalgesia: Replacement of NSAIDs with Phytochemicals. **Nutrients**. 2024, November 15; 16 (22): 3895.

ASSOCIATION BETWEEN VITAMIN B2 INTAKE AND COGNITION AMONG OLDER ADULTS

As the global population ages, cognitive impairment is emerging as a significant health burden. Vitamin B2 is an essential vitamin with intake widely associated with cognitive performance. This study was designed to better understand the association between B2 intake and cognitive performance, including levels above the current Food and Drug Administration recommended level of 1.3 mg/d for men and 1.1 mg/d for women.

This cross-sectional study examined data from two cycles of the National Health and Nutrition Examination Survey (NHANES), conducted between 2011 and 2014. The NHANES uses a sampling design to ensure the representativeness of the non-institutionalized civilian population in the U.S. The data for this study included information from informants over 60 years of age who participated in home interviews and physical assessments. Vitamin B2 intake information was derived from two 24-hour dietary recall interviews, and divided into quartiles; Q1 0.114-1.297 mg/d Q2, 1.297-1.779 mg/d; Q3, 1.781-2.332 mg/d; Q4, 2.333-13.726 mg/d. Cognition was assessed with the Immediate Recall Score Test (IRT), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST).

Data analysis included 2,893 participants, representing approximately 57.08 million individuals in the U.S. In the final, adjusted model, vitamin B2 intake showed a significant association with cognitive performance, including scores on the IRT ($p=0.004$), AFT ($p<0.001$), and DSST ($p=0.001$). Compared to intake below the FDA recommended daily intake, intake above that level was associated with a reduced risk of low cognitive performance (IRT Odds Ratio (OR) 0.66, AFT OR 0.83, and DSST OR 0.65.

Conclusion: This national, cross-sectional study found that dietary vitamin B2 (riboflavin) intake above the RDA protects cognitive health and is negatively associated with the risk of low cognitive performance.

Kangkang, J., et al. Association between Vitamin B2 Intake and Cognitive Performance among Older Adults: A Cross-Sectional Study from NHANES. **Sci Rep.** 2024 Sep 20;14 (1):21930. doi: 10.1038/s41598-024-72949-0

SERUM NEUROFILAMENT AND COGNITIVE PERFORMANCE IN PATIENTS WITH MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

As diffuse axonal injury (DAI) is among the most common consequences of mild to severe traumatic brain injury (msTBI), biomarkers of axonal damage are promising tools for predicting cognitive outcomes. Neurofilament light (NF-L) and phosphorylated neurofilament heavy (pNF-H) are components of axonal cytoskeletons in heavily myelinated axons. This study evaluated the relationship between serum NF-L and pNF-H levels and cognitive recovery over time.

The subjects were 94 patients with msTBI who had survived for at least six months post-injury. Blood was collected for neurofilament measurement up to twice per day during the first week and then biweekly or monthly for approximately one year. Cognitive testing was performed six months post-injury using the California Verbal Learning Test, Second Edition (CVLT-II), the Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency subtest, and the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Processing Speed subtests. Serum NF-L and pNF-H values acquired post-injury were divided into three-time intervals; up to 15 days post-injury (DPI), 16 to 90 DPI, and longer than 90 DPI.

Acute (0 to 15 DPI) NF-L levels were significantly associated with chronic (over 90 DPI) serum neurofilament levels for pNF-H, but not NF-L. The serum levels of pNF-H at 16 to 90 DPI were associated with cognitive outcomes at six months, including cognitive-executive composite scores ($p=0.003$). This association remained after adjustment for age and years of education.

Conclusion: This study of patients with moderate to severe traumatic brain injury found that increased serum levels of phosphorylated neurofilament heavy levels at 60 to 90 days post-injury were associated with worse cognitive executive composite score outcomes at six months.

Trifilio, E., et al. Temporal Profile of Serum Neurofilament Light (NF-L) and Heavy (pNF-H) Level Associations with Six-Month Cognitive Performance in Patients with Moderate-Severe Traumatic Brain Injury. **J Head Trauma Rehab**. 2024, Nov-Dec; 39(6):E470–E480.

TRADITIONAL CHINESE MEDICINE FOR ACUTE INTRACEREBRAL HEMORRHAGE

Acute intracerebral hemorrhage (ICH) is the most serious and least treatable form of stroke. A growing body of evidence supports the use of Chinese herbs to promote reabsorption of the hematoma, reduce perihematomal edema, and enhance the immune system in ICH. FYTF-919 (or Zhongfeng Xingnao oral prescription) is composed primarily of four Chinese herbs, renshen (Panax ginseng), dahuang (Radix et Rhizoma Rhei), Sanqi (Radix notoginseng), and chuanxiong (Rhizoma Logistic chuanxiong),) used in China for the treatment of ICH. This study assessed the effect of these herbs on the outcomes of patients with ICH.

The Chinese Herbal Medicine in Patients with Acute Intracerebral Haemorrhage (CHAIN) study recruited adults with ICH and moderate neurological impairment. Those patients were randomized to receive placebo or FY TF-919, three times per day, beginning within 48-hours of ICH. Follow-up evaluations were undertaken at one, seven, 14, 28, 90, and 180 days. The primary outcome measure was the modified Rankin Scale (mRS) at 90 days.

Data were reviewed for 1,641 adult patients diagnosed with spontaneous ICH. At 90 days, the mRS scores did not differ between groups. In addition, no significant differences were seen between the treatment group and the placebo group in any of the secondary clinical measures (including death) or serious, adverse events.

Conclusion: This study of patients with an acute intracerebral hemorrhage found that treatment with the Chinese herbal compound FYTF-919 had no effect on clinical outcome at 90 days.

Guo, J., et al. Traditional Chinese Medicine FYTF-919 (Zhongfeng Xingnao Oral Prescription) for the Treatment of Acute Intracerebral Haemorrhage: A Multicentre, Randomised, Placebo-Controlled, Double-Blind, Clinical Trial. **Lancet.** 2024, Nov 12: S0140-6736(24) 02261 -X.

LEFT ATRIAL FUNCTION AND VASCULAR BRAIN INJURY

Studies have shown that atrial fibrillation (AF) and ischemic stroke are associated with an increased risk of dementia. In addition, atrial myopathy, is also associated with an elevated risk of dementia, independent of AF and stroke. This study, the Atherosclerosis Risk and Community Study (ARIC), assessed the cross-sectional association between atrial myopathy and vascular brain injury.

The ARIC study included 15,792 adults, 45-64 years of age at the time of recruitment. From this group, 1,488 healthy participants underwent a two-dimensional echocardiogram and a brain MRI. The echocardiogram was used to identify left atrial volume index, left ventricular (LV) ejection fraction (EF), LV mass index, and LA function measures (LA reservoir, conduit, and contractile strain). The subjects were placed into quartiles based on LA reserve. The MRI findings were used to place the subjects into groups including (i) any microbleeds, (ii) subcortical microbleeds, and (iii) lobar microbleeds, as well as (i) any infarcts, (ii) lacunar infarcts, and (iii) cortical infarcts.

Of the 1,488 participants, 23% had one or more cerebral microbleeds. Compared to participants in the highest quartiles of LA reservoir and conduit strain, those in the lowest quartiles had greater odds of one or more subcortical microbleed (Odds Ratios (ORs) 1.60 and 1.55, respectively). Lower LA contractile strain was associated with lower odds of brain infarcts (OR 0.79). No association was found between LA function measures and white matter hyperintensity volume.

Conclusion: This study of adults, free of clinical stroke, dementia, and atrial fibrillation at baseline, found that measures of lower left atrial function were associated with cerebral microbleeds and brain infarcts.

Wang, W., et al. Association of Left Atrial Function with Vascular Brain Injury: The Atherosclerosis Risk in Communities Study. **Euro J Neurol**. 2024, Nov 21: e16549. doi: 10.1111/ ene.16549. Online ahead of print.

NON-FERMENTED VERSUS FERMENTED MILK AND HEART DISEASE

Heart disease is the leading cause of years of life lost globally. Because a healthy diet is essential for the prevention of cardiovascular diseases, specific elements of the diet have been scrutinized. As consumption patterns of different dairy products have changed over the last half century, this study examined effects of fermented and non-fermented milk on the risk of ischemic heart disease (IHD).

Data were obtained from two, population-based studies in Sweden, including the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM). The SMC, established in 1987 to 1990, included all women born from 1914 to 1948 (n=90,303). The COSM was established in late 1997, inviting all male residents born between 1918 and 1952 (n=100,303) to participate. The subjects were asked to participate in surveys covering diet and lifestyle. These included questions regarding milk consumption, including non-fermented milk (3%, 1.5%, or 0.5% fat content) and fermented milk (soured milk and yogurt). The primary outcome variables were the frequency of incident IHD and myocardial infarction.

On average, milk intake did not change after a myocardial infarct (MI) or a new comorbidity. During long-term follow up (22 to 30 years), IHD was found in 17,896 participants. Multivariable analyses found that non -fermented milk intake of more than 1.5 glasses per day was associated with a greater risk of IHD in women ($p<0.001$), but not in men. Similar findings were found for the risk of MI. This increased risk was similar for whole, medium-fat, and low-fat milk. However, the risks of IHD and MI were not affected by the intake of fermented milk in either men or women.

Conclusion: This Swedish study, including data from two large cohort studies, found a direct association between non-fermented milk intake (300mL/day) and ischemic heart disease or myocardial infarction in women, but not men. Fermented milk intake was unrelated to the risk of IHD or MI in either gender.

Michaelsson, K., et al. Non-Fermented and Fermented Milk Intake in Relation to Risk of Ischemic Heart Disease and to Circulating Cardiometabolic Proteins in Swedish Women and Men: Two, Prospective, Longitudinal, Cohort Studies with 100,775 Participants**. BMC Med**. 2024, Nov 8; 22(1): 483.

INFERIOR VENA CAVA FILTERED RETRIEVAL

Approximately 40,000 inferior vena cava filters (IVCFs) are placed in the United States annually. In addition to inconclusive efficacy data, IVCF safety has been questioned due to late mechanical complications. Given these, the U.S. Food and Drug Administration (FDA) has issued communications strongly encouraging IVCF retrieval as soon as clinically feasible. This study was designed to better understand the contemporary use of IVCF and outcomes.

This retrospective observational study included Medicare fee-for-service (FFS) patients who received their first IVCF between January 1, 2013, and December 31, 2021. Insertions and retrievals were identified using current procedural terminology (CPT) codes. Sociodemographics and comorbidities were recorded. Safety events were categorized as periprocedural if they occurred within 30 days of the filter insertion.

During the study, 270,866 patients underwent IVCF insertion. Of these, 14.9% underwent retrieval. At the time of insertion 64.9% were being treated for a first-time venous thromboembolism (VTE), 26.3% for recurrent VTE, and 8.8% for VTE prophylaxis. Between 2013 and 2021, the use of IVCF fell from 157.8 to 64.1 insertions per 100,000 Medicare beneficiaries. During that time, the volume of retrieved filters remained stable, at approximately 4,000 per

year, resulting in an increase in the proportion of filters retrieved, from 8.2% to 19.9%.

Conclusion: This large study, involving elderly Medicare beneficiaries in the United States, found that, despite strong recommendations supporting the routine retrieval of inferior vena cava filters, only 15% were retrieved during follow-up.

Ferro, E., et al. Postmarketing Surveillance of Inferior Vena Cava Filters Among U.S. Medicare Beneficiaries. The SAFE-IVC Study. **JAMA.** 2024. Nov 6:e2419553. doi: 10.1001/jama.2024.19553. Epub ahead of print.

MAJOR VASCULAR EVENTS AFTER FIRST STROKE

Among those with a first ever stroke, the risk of major adverse cardiovascular events (MACE), either nonfatal or fatal is affected by risk factors similar to those of stroke. This study explored the demographic and clinical factors leading to MACE after a first-ever stroke.

Data were obtained from the South London Stroke Register of individuals living with a first-ever stroke. Information was collected from medical records and from patient interviews focused on diagnoses of hypertension, transient ischemic attack, atrial fibrillation, myocardial infarct, diabetes mellitus, and other medical conditions. Patient assessments occurred at stroke onset, at three months, and then annually. Models were constructed to investigate associations between risk factors and outcomes.

Of the 6,051 individuals recruited, the median follow-up time for a MACE was 1.9 years. From 1995-1999 the incidence of stroke recurrence was 11%. Since 2005 this rate has been 7.9%. Admission/ transfer to a stroke unit at the time of index stroke was associated with a 40% lower risk of mortality after a non -fatal event. The risk factors for recurrent stroke were age>85 years ($p<0.001$), having a primary intracerebral hemorrhage ($p=0.02$), a history of MI ($p=0.42$), history of atrial fibrillation ($p<0.001$), smoking ($p=0.04$) and having a stroke that resulted in incontinence ($p=0.04$). The cumulative incidence of MI at 5 years was 1.0% between 1995 and 1999, increasing to 5.8% between 2010 and 2014, and continuing to increase thereafter.

Conclusion: This study found that stroke recurrence decreased in recent years, while post-stroke myocardial infarct rates increased.

Malek, R., et al. Major Vascular Events after First Incident Stroke: A Population-Based Study. **BMJ Neurol Open.** 2024, November;6(2): e000723.

CHRONIC CANNABIDIOL, DAYTIME SLEEPINESS AND FATIGUE IN HYPERTENSIVE PATIENTS

The HYPER-H21-4 trial was a randomized, placebo-controlled trial which assessed the effect of chronic cannabidiol (CBD) supplementation on ambulatory blood pressure (BP) in patients with essential hypertension. This paper presents a prespecified sub-analysis, designed to determine whether chronic CBD supplementation could improve quality of life, anxiety, sleep quality, excessive daily sleepiness, and memory.

The subjects were 64 adults, 40 to 70 years of age, with grade I or grade II hypertension. Those patients were randomized to receive CBD (225 to 450 mg) for five weeks, followed by five weeks of placebo, or vice versa, with a two-week washout between the two. All were assessed with the SF-36, the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the State-Trait Anxiety Inventory (STAI), and the Memory Complaint Questionnaire (MAC-Q).

The CBD group obtained significantly better scores on the ESS ($p= 0.011$), perceived fatigue ($p <0.001$), and psychological well-being scores of the SF-36 ($p=0.039$). No changes were seen in total scores of MAC-Q, PSQI, or STAI. No significant relationships were found between plasma CBD concentrations and any of the scores.

Conclusion: This study of hypertensive patients found that five weeks of CBD administration resulted in decreased daytime sleepiness and perceived fatigue and improved psychological well-being.

Dujic, G., et al. Chronic Cannabidiol Administration Mitigates Excessive Daytime Sleepiness and Fatigue in Patients with Primary Hypertension: Insights from a Randomized, Crossover Trial. **Cannabis Cannabinoid Resch**, 2024, Aug 26. Doi: 10.1089/can. 2024.0028.

HOME BASED TRANSCRANIAL DIRECT CURRENT STIMULATION FOR DEPRESSION

Major depressive disorder (MDD) is a leading cause of years lost to disability worldwide. As transcranial direct current stimulation (tDCS) has shown some benefit for the treatment of MDD, this study investigated the clinical efficacy and safety of the 10-week course of home-based tDCS. The primary outcome measure was the change in depression scores.

The subjects included 174 patients with MDD and a mean age of 37.63 years. Eligible participants were diagnosed with a current depressive episode of at least moderate severity as measured by the Hamilton Depression Rating Scale (HDRS). The subjects were randomly assigned to an active treatment group or a sham treatment group. The tDCS treatment consisted of five, thirty-minute sessions per week for three weeks, followed by three sessions per week for ten weeks, followed by a 10-week open-label phase. For each session, the anode was placed over the left dorsolateral prefrontal cortex and the cathode over the right dorsolateral prefrontal cortex. The primary outcome variable was the change in HDRS scores from baseline to week 10.

Compared to baseline, the mean HDRS scores improved by 9.41 points in the active tDCS group and 7.14 points in the sham tDCS group ($p=0.012$).

Conclusion: This study demonstrates that a 10-week program of at-home transcranial direct current stimulation may improve the symptoms of major depressive disorder.

Woodham, R., et al. Home-Based Transcranial Direct Current Stimulation Treatment for Major Depressive Disorder: A Fully Remote, Phase 2, Randomized, Sham-Controlled Trial. **Nat Med.** 2024 Oct 21. doi: 10.1038/s41591-024-03305-ydoi.org.

YOXINTINE FOR DEPRESSION

Of the traditional Chinese medicines (TCMs), ginseng, and its pharmacologically active ginsenosides, are among those with documented antidepressant activity. Among the metabolic products of ginsenosides, 20(S)-protopanaxadiol (PPD) is thought to have neuroprotective activity. This study

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explored the antidepressant activity of YOXINTINE, a pharmacological agent containing over 98 % of purified PPD.

The subjects were 178 adults with moderate depression who were randomized to receive placebo (P), YOXINTINE, 200mg twice per day (Y-200), or YOXINTINE, 400mg twice per day (Y-400) for eight weeks. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess the severity of depression at baseline and at the end of weeks one, two, four, six, eight, and nine of treatment.

The changes in MADRS scores from baseline were 10.43 in the placebo group, 16.24 in the Y-200 mg group ($p< 0.0001$), and 13.60 in the Y-400 mg group ($p= 0.0013$). The MADRS score reduction in the 200 mg group was greater than that of the 400 mg group ($p= 0.0058$).

Conclusion: This study of adults with moderate depression found that twice per day treatment with 200mg of YOXINTINE (containing 20(S)-protopanaxadiol) resulted in significant improvement of depression scores.

Dong, Z., et al. Efficacy and Safety of YOXINTINE For Depression: A Double-Blinded, Randomized, Placebo-Controlled, Phase2, Clinical Trial. **Phytomed.** 2024; 136: 156204.

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