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WEEKEND WARRIOR AND MILD COGNITIVE IMPAIRMENT

Previous studies have demonstrated that physical activity is protective against physical and cognitive decline. This study explored the efficacy of weekend warrior type activity on the onset of dementia.

The Mexico City Prospective Study included individuals ≥35 years of age recruited from Mexico City, Mexico. A survey was used at baseline (1998-2004) to determine the frequency of participation in exercise or sport, with follow-up surveys a mean of 16 years later. The survey asked about the frequency of participation in exercise or sport, with responses placed in one of four categories. These included, no sport or physical activity (control), once or twice per week (weekend warrior), three or more times per week (regular exercise) or a combination of weekend and regular (mixed). Cognition was measured with the Mini Mental State Exam (MMSE).

Data was available for analysis from 10,033 participants in the repeat survey, with an average age of 51 years. At follow-up there were 2,400 cases of mild dementia. In the adjusted analysis, compared with the control group, the hazard ratio (HR) for mild dementia (≤22 on the MMSE) was 0.75 in the weekend warrior group, 0.89 in the regular exercise group and 0.84 in the mixed group.

Conclusion: This large community-based study found that those who engage in physical activity primarily on the weekend (weekend warriors) have similar reductions in the risk of mild dementia as those who engage in regular activity throughout the week

O'Donovan G, et al., Associations of the 'Weekend Warrior' Physical Activity Pattern with Mild Dementia: Findings from The Mexico City Prospective Study. **Br J Sports Med.** 2025, Feb;59(5):325–332.

OCCASIONAL SMOKING AS A RISK FACTOR FOR MYOCARDIAL INFARCTION

Tobacco abuse is one of the largest threats to public health with more than eight million deaths per year attributed to tobacco abuse. This study addresses the perception by some that smoking a few cigarettes per day carries a relatively low risk for cardiovascular disease.

Data were obtained from the Tromsø Study, a Norwegian prospective cohort study conducted in the municipality of Tromsø, Norway. Seven surveys were conducted between 1974 and 2016 including more than 45,000 subjects, with the present analysis using data from the 2001 and or 2007-8 surveys. Surveys from 15,617 participants were available for this analysis. Information about smoking included questions about daily smoking (Do you/did you smoke daily?' with options 'Yes, now', 'Yes, previously' and 'Never') and occasional smoking ('Do you smoke sometimes, but not daily?' with options 'Yes' and 'No'). Using these data, participants were categorized into four groups (never smokers, former smokers, occasional smokers, and daily smokers). The risk of myocardial infarction (MI) was compared between groups.

A regression analysis found that occasional smoking was associated with a 42% increased risk of MI, compared with never smoking. The results were similar when adjusted for covariates, with a hazard ratio (HR) of 1.41. Comparing the risk by sex, occasional smoking more than doubled the risk of MI in women (HR 2.08), with less effect on men (HR 1.11).

Conclusion: This 20 year follow up of an Italian population-based study found that even occasional tobacco abuse is associated with a significantly elevated risk of a myocardial infarction.

Tiwari, S., et al. Occasional Smoking Is a Risk Factor for Myocardial Infarction in The Population Based Tromso Study, 2001-2021. **Europ J Prevent Cardiol.** 2025, zwaf182: https://doi.org/10.1093/eurjpc/zwaf182.

SUICIDE IN PERSONS DIAGNOSED WITH HEADACHE

Headaches are among the most common and disabling disorders worldwide. Previous research has suggested a link between migraine headaches and attempted suicide. This study was designed to better understand this correlation.

This population-based, cohort study included data from the Danish National Patient Registry and the Danish Psychiatric Central Research Register and completed suicides from the Danish Register of Causes of Death. Data were obtained from the records of 119,486 individuals diagnosed with headaches and 597,430 matched controls. The records from inpatient and outpatient medical encounters were reviewed for migraine, tension-type headache (TTH), and trigeminal autonomic cephalalgia (TAC).

As compared to the control group, the hazard ratio (HR) was elevated in the headache group for attempted suicides (HR, 2.04) and for completed suicides (HR, 1.40). The elevated risk was evident for all headache types. The 15-year adjusted risk (AR) of attempted suicide was 0.78%, among the headache cohort and 0.33% in the control group. The 15-year AR of completed suicide was 0.21% among the headache cohort and 0.15% among the control group. The elevated risk was evident for all headache types.

Conclusion: This population-based cohort study found a robust association between headache diagnosis and attempted and completed suicide across headache types.

Elser, H., et al. Risk of Attempted and Completed Suicide in Persons Diagnosed with Headache. **JAMA Neurol.** 2025, March: 82(3): 276-284.

HOCKEY AND CHRONIC TRAUMATIC ENCEPHALOPATHY

With chronic traumatic encephalopathy (CTE) increasingly recognized in contact sports such as American football, this study was designed to determine whether a similar dose-response association exists among those who participate in ice hockey, where such data were previously limited.

This study utilized a cross-sectional design, analyzing the brains of 77 deceased, male, ice hockey players from the Understanding Neurological Injury and Traumatic Encephalopathy (UNITE) and Framingham Heart Study Brain Banks. Researchers assessed years played of ice hockey, as a proxy for repetitive head impact exposure, examining neuropathological evidence of CTE and its severity through autopsies. Data were gathered from January of 2023 to May of 2024.

The results revealed a strong correlation between the length of ice hockey career and both the presence and severity of CTE. Approximately 19% of those who had played for fewer than 13 years had CTE, with that percentage increasing to 52% for those who had played for 13 to 23 years, and to 96% for those who had played longer. Of professional hockey players examined, 96.4% (27 out of 28) were diagnosed with CTE.

Conclusion: This study found that increased exposure to ice hockey was associated with an increased risk of chronic traumatic encephalopathy.

Anderer, S., et al. Longer Ice Hockey Play Tied to Greater Risk of CTE. **JAMA**. 2025, Feb 4; 333(5): 367.

MEDICATION AND COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

As people with Alzheimer's disease (AD) often have additional morbidities, many have a history of chronic medication use. This study investigated the relationship between medications and cognitive decline in patients with AD.

Data were integrated from two different Swedish registries which included demographics, cognitive testing, and drug use information. Data were reviewed for a cohort including patients diagnosed with AD and mixed dementia between May of 2007 and October of 2018. Medication use was abstracted from pharmacy dispensation records. A cluster analysis was conducted to review the relationship between medication use and cognitive decline, as measured by the Mini-Mental State Examination (MMSE).

Data analyses were completed for 15,428 patients (60.38% women). From these data, four clusters were identified, including high MMSE score without cognitive decline (H-WO), high MMSE score with cognitive decline (H-W), low MMSE score without cognitive decline (L-WO), and low MMSE score with cognitive decline (L-W). Medications which were not prescribed for dementia and were associated with the best cognition cluster (relative to the worst) were atorvastatin (1.44), simvastatin (1.41), warfarin (1.56), zopiclone (1.35), and metformin (2.08). The medications associated with the worst cognitive decline were oxazepam (0.86), paracetamol (0.86), cyanocobalamin (0.86), felodipine (0.79), and furosemide (0.76).

Conclusion: In this study, atorvastatin, simvastatin, warfarin, metformin, and zopiclone presented a positive and statistically significant associations with cognition, while oxazepam, cyanocobalamin, felodipine, furosemide, and paracetamol were associated with worsening cognition.

Grau-Jurado, P., et al. Medications and Cognitive Decline in Alzheimer's Disease: Cohort Cluster Analysis of 15,428 Patients. **J Alz Dis.** 2025, Feb: 103(3): 931-940.

POLYGENIC RISK SCORE AND EFFICACY OF CLOPIDOGREL

After an acute minor stroke or transient ischemic attack (TIA), dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is routinely recommended for secondary stroke prevention. However, the effectiveness of DAPT can be significantly influenced by polymorphisms in genes involved in the metabolism of clopidogrel. This study estimated the impact of multiple single nucleotide polymorphisms (SNPs) on the efficacy of DAPT.

The CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial was a multi-center, double-blind, randomized, clinical trial evaluating the efficacy of DAPT in patients with acute, minor, ischemic stroke or high-risk TIA within 24 hours of onset. This post hoc analysis of the CHANCE study employed high throughput genotyping of SNPs from

blood samples, with 16 being incorporated into the polygenic risk score (PRS) model. The hazard ratio (HR) for the primary efficacy outcome was assessed for each SNP, with the group effect determined by summing the contributions of each.

Data were reviewed from 1,456 subjects in the aspirin alone group and 1,449 in the DAPT group. The participants were divided into three groups based on tertiles of the PRS (low, medium, and high). The occurrence of new stroke within 90 days was 4.9% (23/467) in the low group, 9.5% (44/462) in the intermediate PRS group, and 9.8% (51/520) in the high PRS group (p=0.003). Similar trends were noted for the risk of stroke at one year.

Conclusion: This *post hoc* analysis of the CHANCE trial found that elevated polygenic risk scores were associated with an increased risk of new stroke within 90 days.

Qiu, X, et al. Polygenic Risk Score for the Efficacy of Clopidogrel in Patients with Minor Stroke or Transient Ischemic Attack: A *Post Hoc* Analysis of The CHANCE Trial. **Stroke.** 2025, March; 56(4): 818-827.

DIETARY INFLAMMATORY POTENTIAL AND HEART DISEASE

Coronary heart disease (CHD) affects millions globally, with 197 million cases in 2019, prompting research into how diet and genetics influence its risk. Unhealthy eating habits, such as consuming red meat and sugary drinks, increase inflammation and the risk of CHD. This study explored the effects of dietary inflammatory potential and genetic predisposition on CHD.

The U.K. Biobank cohort was used, including 51,889 participants aged 38 to 73, recruited between 2006 and 2010. The researchers assessed dietary inflammatory potential using the Empirical Dietary Inflammatory Pattern (EDIP) score, derived from 24-hour dietary questionnaires and validated with inflammatory markers (CRP and WBC). Genetic predisposition was measured with a polygenic risk score (PRS), based on 1.7 million genetic variants. Incidents of CHD were tracked via hospital and death records until December of 2022, with Cox regression models adjusting for factors such as age, gender, smoking, and BMI, to better understand associations.

Over 11 years, 1,346 CHD cases emerged. Higher EDIP scores correlated with increased CHD risk per standard deviation, with the highest tertile demonstrating a 26% greater risk than the lowest. In the adjusted analysis the PRS was found to be independently correlated with an increased risk, with a 45% increase per standard deviation above the lowest risk. Jointly, individuals with high EDIP and high PRS had a 3.87-fold increased CHD risk, with absolute risk rising across PRS categories. No significant interaction between EDIP and PRS was found. Anti-inflammatory foods such as fruits and nuts reduced risk.

Conclusion: This study found that inflammation caused by diet was associated with an increased risk of coronary heart disease.

Liu, B., et al. Polygenic Risk Score, Dietary Inflammatory Potential, and Incident Coronary Heart Disease. **Euro J Preventive Cardio.** 2025**.**Advance online publication. https://doi.org/10.1093/eurjpc/zwaf009.

MODERATE CONSUMPTION OF GREEN TEA AND COFFEE FOR THE PREVENTION OF DEMENTIA

The number of people with dementia worldwide is escalating, with 55,000,000 affected in 2019, and expected to rise to 139,000,000 by 2050. As green tea and coffee are thought to have protective effects on cognition, this study was designed to better understand the effect of these two drinks on the risk of dementia.

This cohort study was conducted using 1,155 adults from the Japan Public Health Center-Based Prospective Study (JPHC), initiated in 1990. All completed dietary questionnaires, including information regarding their routine consumption of green tea and coffee, with doses ranging from < one per cup week to 10 or more cups per day. Cognitive function was assessed using the Mini Mental State Examination (MMSE), the Wechsler Memory Scale Revised (WMS-R) Logical Memory subtest, the Clock Drawing Test and the Clinical Dementia Rating (CDR) scale.

Consumption of two to three cups of tea per day was correlated with a significant reduction in the risk of cognitive decline (Odds Ratio (OR) 0.56). Higher doses provided no additional benefit. Those consuming more than one cup of coffee per day had a reduced risk of cognitive decline (OR 0.72), although this finding did not reach statistical significance, and was most pronounced in the elderly.

Conclusion: This longitudinal cohort study of Japanese adults found that moderate green tea consumption in midlife may help prevent dementia, especially in males. The effects of coffee consumption were found to be advantageous only for older adults.

Koreki, A., et al. A Longitudinal Cohort Study Demonstrating the Beneficial Effect of Moderate Consumption of Green Tea and Coffee on the Prevention of Dementia: The JPHC Saku Mental Health Study. **J Alz Dis.** 2025, Jan; 103(2): 519-527.

COVID VACCINE EFFECTIVENESS

The XBB.1.5 Omicron variant of the SARS-CoV-2 virus has been the target of vaccines from Pfizer-BioNTech and Moderna, approved in September 2023. That month the CDC recommended the updated 2023-2024 monovalent XBB.1.5 COVID-19 vaccines for all individuals aged six months and older. Despite this, fewer than one quarter of U.S. adults received the vaccine, allowing for real-world studies to assess its effectiveness.

The Veterans Health Administration (VHA) emulated a target randomized controlled trial of XBB.1.5 COVID-19 vaccination versus no XBB.1.5 COVID-19 vaccination. The researchers executed seven sequential trials, each having a two-week enrollment period, to account for multiple potential enrollment times for those who did not receive COVID-19 vaccination, matching each eligible vaccinated person to one unvaccinated person. The three primary outcomes were SARS-CoV-2 infection (S-I), SARS-CoV-2-associated hospitalization (S-H), and SARS-CoV-2-associated deaths (S-D).

During the study, 587,137 (239,539 Pfizer and 347,598 Moderna) vaccine recipients were matched to 587,137 unvaccinated veterans. The average age of participants was 69.9 years. During a mean follow-up of 176 days, there were 8,028 SARS-CoV-2 infections in the vaccinated group and 7,946 in the unvaccinated group. SARS-CoV-2 related hospitalizations occurred in 650 of the vaccinated group and 823 of the unvaccinated group. SARS-CoV-2 related deaths occurred in 109 of the vaccinated group and 147 of the unvaccinated group. The

effectiveness of the vaccines waned over time since injection.

Conclusion: This large study from the Veterans Health Association care system found that the COVID-19 vaccines targeting the XBB.1.5 variant of Omicron was not effective in preventing COVID infections but had a small protective effect against hospitalization or death.

Ioannou, G., et al. Effectiveness of the 2023-to-2024 XBB.1.5 COVID-19 Vaccines over Long-Term Follow-up. **Ann Int Med.** 2025, March; 178 (3): 348-360.

AGE AND NEUROLOGIC MANIFESTATIONS OF LONG COVID

As of October of 2024, more than 776 million total cases and over seven million deaths have been reported since the beginning of the global coronavirus disease-2019 (COVID-19). Symptoms resolve in most, but may persist, with 15% of patients continuing to report symptoms 12 months after the initial infection. This syndrome has been called “post-COVID-19 condition”, “post-acute sequelae of SARS-CoV-2 infection (PASC)”, or, more commonly, “long COVID.” The neurologic manifestations of PASC are known as Neuro-PASC. This study was designed to characterize the neurologic manifestations of Neuro-PASC across the adult lifespan.

This retrospective review included patients seen at the Neuro- COVID-19 Clinic of Northwestern Memorial Hospital, including 1,300 patients who tested positive for SARS-CoV-2 between May of 2020 and March of 2023. These included 200 post-hospitalization Neuro-PASC (PNP) and 1,100 non-hospitalized Neuro-PASC (NNP). The subjects were divided into younger (18 to 44 years), middle-age (45 to 64 years), and older (65+ years) groups. Neurologic symptoms, comorbidities, fatigue, sleep disturbance, and cognitive performance were assessed using the PROMIS and NIH toolbox measures. Clinical outcomes were compared by age.

While older individuals had more comorbidities and abnormal neurologic findings, younger and middle-age groups reported higher neuro-PASC symptom burden including fatigue (p=0.04), and sleep disturbance (p=0.002). Younger NNP patients exhibited the worst executive function (p=0.01) and working memory (p=0.0002) skills, as compared to the other groups.

Conclusion: This study found that, among patients who have COVID-19 infections, younger patients tend to be more susceptible to long COVID with neurologic manifestations.

Choudhury N., et al. Neurologic Manifestations of Long COVID Disproportionately Affect Young and Middle-Age Adults. **Ann Neurol.** 2025, Feb;97(2):369-383.

MRI BIOMARKER TO PREDICT FUNCTIONAL OUTCOME AFTER ENDOVASCULAR THROMBECTOMY

Endovascular thrombectomy (EVT) has dramatically improved the treatment of large vessel occlusion (LVO). However, a post-EVT imaging biomarker of functional outcome has not been well established. This study was designed to validate a novel magnetic resonance imaging-based metric, infarct density, as a marker of infarct severity.

The subjects were adult patients (≥18 years) with LVO in the anterior circulation who underwent EVT within 24 hours of stroke onset and who successfully achieved reperfusion (modified Thrombolysis in Cerebral Infarction (mTICI) ≥2b). Clinical data from the charts included demographics, medical history, occlusion location, and procedural details, including final mTICI score. The MRI data were used to quantify the proportion of the infarct with a very low ADC value (<470 10^{-6} mm^2/s). This was compared to the functional outcome.

Data were analyzed from the records of 272 patients. A good functional outcome (a 90-day mRS score of ≤2) was achieved in 62% of the cohort. After adjusting for clinical and radiographic factors, the final infarct volume (FIV) and infarct density were both independently inversely associated with good outcome (p=0.003 and p<0.001 respectively). The final model incorporating both FIV and infarct density achieved excellent classification performance (hazard ratio, 0.87).

Conclusion: This study found that infarct density provides an MRI-based measure of stroke severity that is independently and strongly associated with functional outcome.

Favilla, C., et al. Validation of a Novel Magnetic Resonance Imaging Biomarker of Infarct Severity to Predict Functional Outcome after Endovascular Thrombectomy. **Stroke.** 2025, April; 45(4): 926-936.

NEUROMODULATION FOR PEDIATRIC CEREBRAL PALSY

For children with unilateral cerebral palsy (UCP), effective interventions for improving physical disability have been elusive. This study evaluated the efficacy of transcranial direct current stimulation (tDCS) to enhance motor function in patients with UCP.

This double-blind, randomized, multicenter, sham-controlled, phase three trial enrolled 89 patients between ages of six and 18 with UCP. All subjects were involved in a 10-day motor learning camp, involving constraint induced therapy (CIT), 7.5 hours per day. The subjects were randomly assigned to receive either placebo or tDCS, using one milliampere applied to the contralesional motor cortex. The primary endpoints were changes from baseline to six months in hand function and functional goals, assessed using the Assisting Hand Assessment and Canadian Occupational Performance Measure.

Data analyses were completed for 83 patients, of whom 42 were in the sham group and 41 in the active treatment group. At six months, the mean changes in the AHA were significant for both groups, with a gain of 5.2 for the sham group and 4.6 for the tDCS group (p=0.63). The proportion achieving sustained clinical significance of more than five points included 48.8% of the sham group and 50% of the tDCS group.

Conclusion: This study of patients with cerebral palsy found that constraint induced therapy could significantly improve the function of the affected arm, with residual effects up to six months, but with no additional improvement using adjunct transcranial direct current stimulation.

Hilderley, A., et al. Neuromodulation for Children with Hemiparesis and Perinatal Stroke. **JAMA Neurol.** doi:10.1001/jamaneurol.2024.4898.

LEGUME-BASED DIETARY INTERVENTION

The prevalence of type-2 diabetes (T2D) worldwide has increased by four-fold in the last four decades. Many studies support the use of food-based interventions as a promising

approach to improve metabolic health and reduce the risk of T2D and cardiovascular disease (CVD). This study explored the benefits of a food-based, portion-controlled, intervention diet, consisting of legumes as the main protein.

The subjects were 127 prediabetic adults, randomized to receive either a control group (CG) diet or an intervention group (IG) diet for 16 weeks. Both groups were provided with calorie-restricted diets, served in two meals per day, with comparable nutritional composition except for the inclusion of 100 g of cooked legumes per meal for the IG group, and a chicken-based diet for the CG. Blood and fecal samples were collected at multiple time points to assess glycemic markers, lipid profiles, anthropometrics, and gut microbiome composition.

Both groups showed weight loss (5.1% IG, 4.3% CG) and improved lipid profiles, with greater improvements in the IG for levels of total cholesterol ($p<0.001$) and high-density lipoprotein cholesterol at week four ($p<0.001$). In addition, the IG group had significantly lower low-density lipoprotein cholesterol levels at week 12 ($p<0.001$) and greater reductions in HbA1c at week 16 ($p=0.004$). The analysis of the gut microbiome found significant increases in species belonging to the class *Clostridia* (*Eubacterium rectale*, *Roseburia faecis*, and *Roseburia hominis*), as well as the *Bifidobacterium* genus under the phylum *Actinobacteria.*

Conclusion: This study found that a diet rich in legumes, healthy vegetable oils, and spices, and low in carbohydrates can improve cardiometabolic health beyond the effects which could be achieved through calorie restriction alone.

Wu, X., et al. A Legume-Enriched Diet Improves Metabolic Health in Prediabetes Mediated Through Gut Microbiome: A Randomized Controlled Trial. **Nat Commun**. 2025, Jan 22; 16: 942.

LOW-LOAD BLOOD FLOW RESTRICTION TRAINING AND HIGH-LOAD RESISTANCE TRAINING

This research examined the effects of low-load blood flow restriction training (LL-BFRt), sham LL-BFRt, and high-load resistance training (HL-Rt) on quadriceps strength, dynamic stability, and functional performance among basketball and rugby players in Bali, Indonesia. The study was motivated by the need to address deficits in quadriceps muscle strength and dynamic stability, in an effort to prevent injuries in athletes.

The study involved 63 eligible participants who were randomly assigned to three intervention groups, LL-BFRt, sham LL-BFRt, and HL-Rt. The LL-BFRt involved using pneumatic cuffs set at 70% limb arterial occlusion pressure (LAOP) while performing eccentric exercises at 30% one-repetition maximum (1RM). Sham LL-BFRt used cuffs set at 10% LAOP with the same exercises, and HL-Rt performed exercises at 70% 1RM without cuffs. Each participant underwent 45-minute training sessions twice per week for eight weeks. Quadriceps strength (QS), the Star Excursion Balance Test (SEBT), and the Single-Leg Hop Test (SLHT) were performed at baseline, four weeks, and eight weeks.

Compared to baseline measures, significant improvements were noted in QS, SEBT and SLHT in LL-BFRt and HL-Rt groups ($p<0.05$) for both comparisons. In addition, compared to the sham LL-BFRt group, improvements were greater in the LL-BFRt group for QS, SEBT and SLHT ($p< 0.05$ for all comparisons) and HL-Rt groups for QS, SEBT and SLHT ($p < 0.05$ for all comparisons). No significant differences were noted between LL-BFRt group and HL-Rt group.

Conclusion: This study concluded that low load blood flow restriction resistance training and high load resistance training are comparable in improving quadriceps strength, dynamic stability, and functional performance, suggesting that low load training may be preferable for those who should avoid high loads.

Adhitya, I. Effect of Low-Load Blood Flow Restriction Training and High-Load Resistance Training on Quadriceps Strength, Dynamic Stability, and Functional Performance. **Clin J Sports Med.** 202500, 1-9. http://dx.doi.org/10.1097/JSM.0000000000001330.

TERIPARATIDE, DENOSUMAB AND BIPHOSPHONATES FOR OSTEOPOROSIS

With the aging of the world's population, an increase is expected in age-related diseases including osteoporosis. Since the 1990s bisphosphonates (BPs) have been the first line pharmaceutical treatment for osteoporosis. Since then, additional medical options have become available. This study compared the efficacy of teriparatide and denosumab to that of bisphosphonates.

This literature review scanned the published medical literature through May 31, 2023. Eligible studies included randomized controlled trials involving patients with osteoporosis, comparing those treated with BPs to either teriparatide, or denosumab.

The search identified 23 studies to include in the meta-analysis. Of these 15 trials, involving 6,264 patients, assessed the risk of fracture. Those comparing parathyroid with BPs found that those treated with teriparatide had a greater reduction in fracture occurrence with the relative risk (RR) 0.61, ($p<0.001$). The studies comparing denosumab and BPs found equivalent reductions in fractures (RR 0.99, $p = 0.96$). Studies focusing on the gain in BMD found that, compared to treatment with denosumab, treatment with teriparatide resulted in a greater improvement in BMD ($p=0.001$).

Conclusion: This literature review and meta-analysis of medications used for the treatment of osteoporosis found the reduction in the risk of fractures was greater among those treated with teriparatide compared to bisphosphonates and denosumab.

Li, M., et al. Efficacy and Safety of Teriparatide Vs. Bisphosphonates and Denosumab Vs. Bisphosphonates in Osteoporosis Not Previously Treated with Bisphosphonates: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. **Arch Osteoporosis.** 2024, Sep 23;19(1):89.

METABOLOMIC PATHWAYS HEALTHY AGING INDEX AND MORTALITY

Studies of metabolic dysfunction during aging have suggested a potential functional role for metabolites as initiators or propagators of aging biology. This paper reviews the metabolic associations of the healthy aging index (HAI), which includes five easily measured physiologic traits (cardiovascular, metabolic, lung, renal function and cognitive function).

The Health Aging and Body Composition (ABC) study is a prospective cohort of mobile adults 70-79 years of age recruited from March 1997 to July of 1998. Of those selected for metabolic profiling, 2,015 had information for HAI at year one (1997-1998). Metabolites in plasma were measured at the year two visit to quantify metabolites. Metabolite profiling was performed, with 442 unique metabolites quantified. An HAI was constructed in year one and year 10. A standard regression was used to identify metabolomic correlates of year one and year 10 HAI, change in HAI over time, and mortality.

The analysis identified 42 metabolites associated with change in HAI over time. Researchers identified that 13 lipids, 4 amino acids, and 4 metabolites of other classes were associated with worse and worsening HAI while 20 lipids and 1 amino acid was associated with better and improving HAI.

Conclusion: This study identified patterns of circulating metabolites that were associated with physiological aging, reinforcing data of a metabolic foundation of biological aging.

Yao, S., et al. Metabolomic Pathways of Inflammation and Mitochondrial Dysfunction are Related to Worsening Healthy Aging Index and Mortality. **J Gerontol A Biol Sci Med Sci.** 2025. doi; 10.1093/gerona/glaf057. Online ahead of print.

DUAL SENSORY IMPAIRMENT AND DEMENTIA

Globally, 55,000,000 individuals are diagnosed with dementia with 10 million new cases expected annually. It is therefore important to identify factors which could delay or prevent the onset of dementia. As sensory impairment increases with age, this study reviewed the correlation between dual sensory impairment (DSI) and the development of dementia.

This systematic review and meta-analysis included a review of literature using the Medline Embase and Cochrane Library databases through July 8, 2024. Studies were identified which focused on sensory impairment with dementia as an outcome variable. The literature review identified 10 cohort studies and one case control study for use in the review and meta-analysis.

A total of 11 observational studies with 346,659 participants were included. Ten of the studies investigated the association between DSI and all-cause dementia, four studies investigated the association between DSI and incident AD, and two studies investigated the association between DSI and incident vascular dementia (VaD). The analysis found that, compared with no sensory impairment, DSI was associated with an increased incidence of dementia (hazard ratio (HR): 1.46). This association was found for different types of dementia including AD (HR 2.07) but not VaD. Single sensory impairment was also associated with the risk of dementia, including only vision impairment (HR 1.29) or only hearing impairment (HR 1.18).

Conclusion: This systematic review and meta-analysis found that those with dual sensory impairment had a 46% greater risk of dementia compared with those with no sensory impairments.

Yoshida Y. et al. The Association Between Dual Sensory Impairment and Dementia: A Systematic Review and Meta-Analysis. **J Alzheimer's Disease.** 2025, February;103(3):637-648.

POSTMENOPAUSAL FRACTURE WITH INFREQUENT ZOLEDRONATE

At menopause, women have a remaining lifetime risk of fracture of more than 50%. Most fracture prevention strategies focus on persons at highest risk for fracture, though this focus is limited in that only 20% of fractures occur in women with a bone mineral density (BMD) that indicates osteoporosis. Zoledronate has a prolonged effect on BMD and bone turnover, making it a potential treatment for preventing early postmenopausal bone loss.

This study recruited postmenopausal women 50 to 60 years of age, randomly selected from the population of Auckland, New Zealand. The women were randomly assigned to receive zoledronate 5 mg at baseline and again at five years (zoledronate–zoledronate group), an infusion of zoledronate at a dose of 5 mg at baseline and an infusion of normal saline at five years (zoledronate–placebo group), or infusions of normal saline at baseline and at five years (placebo–placebo group). The primary endpoint was a new vertebral fracture determined using spine radiographs, with secondary endpoints including fragility fractures, any fracture, and major osteoporotic fractures. All underwent clinical assessments at baseline, five years and 10 years.

Of the 1,054 women enrolled, 95.2% completed the 10-year study. Compared to the placebo–placebo group, the relative risk of any fracture was 0.70 in the zoledronate–zoledronate group and 0.77 in the zoledronate–placebo group. The differences in the percent change in BMD between each of the zoledronate groups and the placebo–placebo group were approximately five to nine percentage points at 10 years.

Conclusion: This study of postmenopausal women found that a single infusion of zoledronate could significantly reduce the risk of subsequent fractures.

Bolland, M., et al. Fracture Prevention with Infrequent Zoledronate in Women 50 To 60 Years of Age. **N Engl J Med**. 2025, January; 392(3), 239-248.

TACKLING TECHNIQUE AND CONCUSSION

Concussions pose a significant health risk in high-contact sports, including American football. This study was conducted to identify tackling techniques and characteristics linked to concussions in National Football League (NFL) tacklers.

This study used a matched case-control study design, utilizing qualitative video reviews of NFL games from the 2015-2019 seasons to compare tackling techniques between 51 concussed tacklers (cases) and 96 non-concussed tacklers (controls). Data were sourced from the NFL's electronic medical record system and Next Gen Stats, focusing on 1-on-1 tackles during pass and rush plays. Video analysis coded 20 tackling characteristics, such as tackle type and head placement, using multiple high-quality camera angles, with statistical analysis via conditional logistic regression to assess concussion risk, adjusted for closing velocity.

The analysis identified 12 tackling techniques significantly associated with concussion risk, with helmet-to-helmet tackles posing the highest risk, followed by front tackles doubling the risk compared to side tackles, and no concussions recorded in from-behind tackles. Incorrect head placement increased the risk nearly fourfold, while targeting the ball

carrier's torso reduced risk. Higher closing speeds significantly amplified concussion likelihood.

Conclusion: This study used video of NFL games to identify tackling techniques associated with a greater risk for concussion.

Sherwood, C. P., et al. Tackle Techniques and Characteristics Associated with a Concussion in Tackling Players in the National Football League. **Am J Sports Med.** 2025. Advance online publication. https://doi.org/10.1177/03635465251321005.

SMALL VESSEL DISEASE PROGRESSION AND COGNITIVE DECLINE

Recent research studies have concentrated on the influence of small vessel disease (SVD) on the advancement of dementia. This study investigated the associations between individual markers of SVD and longitudinal cognitive decline.

The data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The database, started in 2003, includes adults diagnosed as cognitively normal (CN) and with MCI. A cognitive battery assessed cognitive function at 12 and 24 months. Brain magnetic resonance imaging (MRI) was obtained at baseline, and at one year, and two years. These were reviewed to assess white matter hyperintensity (WMH), cerebral microbleeds (CBs), enlarged perivascular space, and overall small vessel disease (SVD) burden in deep and periventricular tissue.

Data were analyzed from 151 participants in the CN group and 281 participants in the MCI group. In the CN group, CB progression was associated with a decline in language function ($p<0.05$), while the progression of deep WMH progression was associated with a decline in memory function ($p<0.05$). In the MCI group, CMB progression was associated with a decline in memory function ($p<0.05$) while the progression of lacunes was associated with a decline of executive function ($p<0.05$). The progression of global SVD score was not correlated to longitudinal cognitive function.

Conclusion: This study of cognitively normal adults and adults with mild cognitive impairment found that cognitive decline was associated with individual markers of small vessel disease (cerebral microbleed, white matter hyperintensity and lacunar infarcts) rather than a global measure of small vessel disease.

Wang. J., et al. Association of Small Vessel Disease Progression with Longitudinal Cognitive decline Across Mild Cognitive Impairment. **J Alz Disease**. 2025;103(3): 714-723.

GLP-1 AGONISTS FOR PARKINSON'S DISEASE

Parkinson's disease (PD) presents a significant public health concern as a progressive neurodegenerative disorder with no known cure or treatment. Recent studies have indicated that Glucagon-like peptide receptor agonists (GLP1-RAs) may be able to improve motor and cognitive functions in patients with PD. This study investigated the influence of GLP-1RA on the development of PD in a real-world clinical practice.

This nationwide cohort comprised 33,462 patients enrolled from 2007 to 2018 and followed until 2022, with 16,731 initiators of GLP-1RA and 16,731 initiators of the comparator drug, dipeptidyl peptidase-4 inhibitors (DPP-4i). The subjects were patients >50 years of age, with no history of cancer or PD, who had never taken either study drug. Those participants were followed until a diagnosis of PD, death, emigration, 10 years after study entry, or the end of the study.

At ten-year follow-up, 192 patients developed PD. Compared to those who were prescribed DPP-4i, those prescribed GLP1-RAs had a decreased risk of developing PD (Hazard ratio, 0.57). Similar trends were found when using insulin as a comparator drug.

Conclusion: This nationwide study found that the use of GLP-1RAs was associated with reduced risk of Parkinson's disease.

Gamborg, M., et al. GLP-1 Agonists as Potential Neuromodulators in Development of Parkinson's Disease: A Nationwide Cohort Study. **Euro J Neurol,** 2025; Feb;32(2):e70075.

BIOLOGICAL CLOCKS, VITAMIN D, OMEGA-3 AND EXERCISE

Epigenetic clocks are DNA methylation algorithms that combine information from measurements across the genome to quantify variations in biological compared to chronological aging. Four such clocks have been studied (PhenoAge, GrimAge, GrimAge2 and DunedinPACE). This study assesses the effect of vitamin D supplementation, omega-3 supplementation and simple home exercise on biological aging.

The DO-HEALTH Bio-Age Trial included 777 participants with DNA measures at baseline and at three years. Enrollees were healthy and active adults 70 years of age and older across five countries in Europe. The study used a 2x2x2 factorial design to test the effects of 2,000 international units per day of vitamin D, 1g per day of omega-3 and three 30-minute exercise sessions per week. Participants were randomized to one of eight treatments arms, all followed with yearly examinations and phone calls every three months. Blood was collected at baseline and up to three years follow up.

Daily omega-3 supplementation reduced the pace of biologic aging values as measured by PhenoAge, GrimAge2 and DunedinPACE. Vitamin D supplementation and SHP were not associated with changes in any of the clocks. Using the PhenoAge, there was evidence of additive treatment effects for combinations of omega-3 supplementation with the other two interventions individually and together.

Conclusion: This study found that omega-3 reduced the rate of biological aging.

Bischoff-Ferrari, H., et al. Individual and Additive Effects of Vitamin D, Omega-3 and Exercise on DNA Methylation Clocks of Biological Aging in Older Adults from the DO-HEALTH Trial. Nat Aging. 2025, Mar;5(3):376-385.

ABSENCE OF CARE AMONG THOSE WITH COGNITIVE AND PHYSICAL LIMITATIONS

The World Health Organization estimates that 16% of the global population experiences disabilities, many of whom face functional limitations that impact daily living. Despite the critical need for caregiving, the global patterns of care received by people living with disabilities (PLWD) remain poorly understood. This study explored caregiver trends across multiple countries.

Data were obtained from the Health and Retirement Study (HRS) of the United States, the English Longitudinal Study of Aging (ELSA), the Survey of Health, Aging and Retirement in Europe (SHARE) and

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the China Health and Retirement Longitudinal Study (CHARLS). These data were reviewed to examine trends of caregiving and caregiver gaps among PLWD.

The prevalence of PLWD receiving no care for activities of daily living (ADLs) and Instrumental Activities of Daily Living (IADL) was high, with 48.5% of person-waves in ELSA and 63.1% in CHARLS received no care at all for ADLs. Similarly, more than a third of HRS (39.0%) and SHARE (38.4%) reported receiving no care for ADLs. The data also demonstrated that PLWD and living alone experience significantly larger gaps in informal care compared to those living with others.

Conclusion: This study reviewed longitudinal data from United States, Europe, and China demonstrating that at least one in five people living with disability receive no care for their activities of daily living, and the absence of care has not improved over time.

Lin, Z., et al. Absence of Care Among Community Dwelling Older Adults with Dementia and Functional Limitations. **Nat Aging**. 2025; https://doi.org/10.1038/s43587-025-00836-y

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