GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Diagnosis and Treatment of Chronic Fatigue Syndrome/Myalgic Encephalopathy (CFS/ME) [Internet].

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Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); **2006**. Report from Norwegian Knowledge Centre for the Health Services (NOKC) No. 09-2006.

Norwegian Institute of Public Health (NIPH) Executive Summaries. Link to NIPH Systematic Reviews.

Aim: To assess and synthesize the evidence base for diagnosing and treating chronic fatigue syndrome/myalgic encephalopathy (CFS/ME).

Methods: The overview of the scientific knowledge is based on systematic reviews and a search of recent primary and qualitative studies. The assessment was done stepwise, starting with 1168 abstracts and ending with 6 systematic reviews, 5569 abstracts of RCTs/CCTs and ending with 4 RCTs on adults and 3 RCTs on children/adolescents. We identified 807 qualitative studies and included 18. Level of documentation was based on GRADE. A review team performed the assessment, with input from 2 patient organizations. The literature was searched via the Cochrane Database of Systematic Reviews, DARE, MEDLINE, EMBASE, PsycINFO, and AMED. Patients with CFS, ME, postviral fatigue syndrome, and chronic fatigue and immunodysfunctional syndrome were included. Interventions included any kind of treatment for CFS/ME. All outcomes were considered, and fatigue, physical and mental health, and quality of life are reported.

Results: *Diagnosis:* The recommendations for diagnosis are based on guidelines for clinical diagnosis of CFS/ME published by British, Australian, Canadian, and other groups. Patient history includes extreme fatigue lasting at least 6 months triggered by disproportional demands, and is unpredictable, does not improve by rest, or is worsened by physical or mental effort. Other symptoms are, *e.g.*, sore throat, swollen lymph nodes, painful joints and muscles, headache, and sleeping problems. Comorbidities may include fibromyalgia or irritable bowel syndrome. The course varies. Differential diagnoses, *e.g.*, metabolic diseases, diabetes, coeliac disease, cancer, bipolar or depressive conditions, neurological disease, and Addison's disease must be ruled out. No diagnostic test can verify the diagnosis, nor point to the best treatment. *Treatment:* Cognitive behavioral therapy, graded exercise therapy, pharmacological treatment, immunological treatment, supplements and alternative/complementary treatment. Documentation is low or very low for most outcomes: Cognitive behavioral therapy suggests improved physical function and quality of life, but it is uncertain if the treatment influences mental health. Graded exercise therapy suggests reduced fatigue, but effects on depression or quality of life are not documented. Dropout was high, especially with high-intensity exercise. No evidence recommends pharmacological treatment unless there is relevant comorbidity. Immune modulating treatment has uncertain effects, but could have serious adverse effects. Effects of supplements and alternative/complementary medicine are uncertain. Few studies investigated the effects of treatment in children and adolescents. No studies investigated the effects of treatment in the severely ill or disabled.

Further research/reviews required: Studies on better treatment for severely ill or disabled sufferers are insufficient. Evidence on children and adolescents is scarce, and for adults the level of documentation is low or very low. Diagnostic criteria vary by study, making comparisons difficult. Empirical studies on treatment experiences are missing. CFS/ME symptoms are subjective. Qualitative studies show that patients feel stigmatized and mistrusted, and doctors find it challenging to diagnose and treat CFS/ME. The prevalence, prognosis, and cause of CFS/ME remain unclear. More research is needed.

HEADACHE and MIGRAINE

The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial.

Krøll LS[1,2], Hammarlund CS[1], Linde M[3], Gard G[1], Jensen RH[2].

Cephalalgia. **2018 Jan 1**:333102417752119. doi: 10.1177/0333102417752119. [Epub ahead of print]

Aim To evaluate aerobic exercise in migraine and co-existing tension-type headache and neck pain.

Methods Consecutively recruited persons with migraine and co-existing tension-type headache and neck pain were randomized into an exercise group or control group. Aerobic exercise consisted of bike/cross-trainer/brisk walking for 45 minutes, three times/week. Controls continued usual daily activities. Pain frequency, intensity, and duration; physical fitness, level of physical activity, well-being and ability to engage in daily activities were assessed at baseline, after treatment and at follow-up.

Results Fifty-two persons completed the study. Significant between-group improvements for the exercise group were found for physical fitness, level of physical activity, migraine burden and the ability to engage in physical activity because of reduced impact of tension-type headache and neck pain. Within the exercise group, significant reduction was found for migraine frequency, pain intensity and duration, neck pain intensity, and burden of migraine; an increase in physical fitness and well-being.

Conclusions Exercise significantly reduced the burden of migraine and the ability to engage in physical activity because of reduced impact of tension-type headache and neck pain. Exercise also reduced migraine frequency, pain intensity and duration, although this was not significant compared to controls. These results emphasize the importance of regular aerobic exercise for reduction of migraine burden.

The association of neurologists with headache health care utilization and costs.

Callaghan BC[1], Burke JF[2], Kerber KA[2], Skolarus LE[2], Ney JP[2], Magliocco B[2], Esper GJ[2].

Neurology. **2018 Jan 10**. pii: 10.1212/WNL.0000000000004925. doi: 10.1212/WNL.0000000000004925. [Epub ahead of print]

OBJECTIVE: To determine the association of a neurologist visit with headache health care utilization and costs.

METHODS: Utilizing a large privately insured health care claims database, we identified patients with an incident headache diagnosis (ICD-9 codes 339.xx, 784.0x, 306.81) with at least 5 years follow-up. Patients with a subsequent neurologist visit were matched to controls without a neurologist visit using propensity score matching, accounting for 54 potential confounders and regional variation in neurologist density. Co-primary outcomes were emergency department (ED) visits and hospitalizations for headache. Secondary outcomes were quality measures (abortive, prophylactic, and opioid prescriptions) and costs (total, headache-related, and non-headache-related). Generalized estimating equations assessed differences in longitudinal outcomes between cases and controls.

RESULTS: We identified 28,585 cases and 57,170 controls. ED visits did not differ between cases and controls ($p = 0.05$). Hospitalizations were more common in cases in year 0-1 (0.2%, 95% confidence interval [CI] 0.2%-0.3% vs 0.01%, 95% CI 0.01%-0.02%; $p < 0.01$), with minimal differences in subsequent years. Costs (including non-headache-related costs) and high-quality and low-quality medication utilization were higher in cases in the first year and decreased toward control costs in subsequent years with small differences persisting over 5 years. Opioid prescriptions increased over time in both cases and controls.

CONCLUSION: Compared with those without a neurologist, headache patients who visit neurologists had a transient increase in hospitalizations, but the same ED utilization. Confounding by severity is the most likely explanation given the non-headache-related cost trajectory. Claims-based risk adjustment will likely underestimate disease severity of headache patients seen by neurologists.

HEADACHE and MIGRAINE (Continued)

Genetic association of HCRTR2, ADH4 and CLOCK genes with cluster headache: a Chinese population-based case-control study.

Fan Z[1,2], Hou L[1], Wan D[1], Ao R[1], Zhao D[1], Yu S[3].

J Headache Pain. **2018 Jan 9**;19(1):1. doi: 10.1186/s10194-017-0831-1.

BACKGROUND: Cluster headache (CH), a rare primary headache disorder, is currently thought to be a genetic susceptibility which play a role in CH susceptibility. A large numbers of genetic association studies have confirmed that the HCRTR2 (Hypocretin Receptor 2) SNP rs2653349, and the ADH4 (Alcohol Dehydrogenase 4) SNP rs1126671 and rs1800759 polymorphisms are linked to CH. In addition, the CLOCK (Circadian Locomotor Output Cycles Kaput) gene is becoming a research hotspot for CH due to encoding a transcription factor that serves as a basic driving force for circadian rhythm in humans. The purpose of this study was to evaluate the association between CH and the HCRTR2, ADH4 and CLOCK genes in a Chinese CH case-control sample.

METHODS: We genotyped polymorphisms of nine single nucleotide polymorphisms (SNPs) in the HCRTR2, ADH4 and CLOCK genes to perform an association study on a Chinese Han CH case-control sample (112 patients and 192 controls), using Sequenom MALDI-TOF mass spectrometry iPLEX platform. The frequencies and distributions of genotypes and haplotypes were statistically compared between the case and control groups to identify associations with CH. The effects of SNPs on CH were further investigated by multiple logistic regression.

RESULTS: The frequency of the HCRTR2 SNP rs3800539 GA genotype was significantly higher in cases than in controls (48.2% vs.37.0%). The GA genotypes was associated with a higher CH risk (OR = 1.483, 95% CI: 0.564-3.387, p = 0.038), however, after Bonferroni correction, the association lost statistical significance. Haplotype analysis of the HCRTR2 SNPs showed that among eight haplotypes, only H1-GTGGGG was linked to a reduced CH risk (44.7% vs. 53.1%, OR = 0.689, 95% CI =0.491~0.966, p = 0.030). No significant association of ADH4, CLOCK SNPs with CH was statistically detected in the present study.

CONCLUSIONS: Association between HCRTR2, ADH4,CLOCK gene polymorphisms and CH was not significant in the present study, however, haplotype analysis indicated H1-GTGGGG was linked to a reduced CH risk.

CHRONIC PAIN

The relationship between concomitant benzodiazepine-opioid use and adverse outcomes among U.S. veterans.

Gressler LE[1], Martin BC[1], Hudson TJ[2,3], Painter JT[1,2].

Pain. **2017 Nov 20**. doi: 10.1097/j.pain.0000000000001111. PMID:29189516. [Epub ahead of print]

Benzodiazepines and opioids are commonly used among Veterans suffering from mental health disorders and pain conditions. The objective of this study is to determine if concomitant benzodiazepine-opioid use increases the incidence of adverse outcomes above the baseline risk of non-acute opioid only use. The dataset contained all Veterans who filled at least one opioid prescription during the years 2008 to 2012. Non-acute opioid use was defined as having opioid prescriptions greater than or equal to 20 days within a 60-day period. Concomitant use was defined as having opioid and benzodiazepine prescriptions that overlapped for at least seven days. Non-acute opioid only users were matched to concomitant opioid-benzodiazepine users based on propensity scores. A 365-day observation period was used to identify adverse outcomes. The primary outcome examine the existence of one or more of the following outcomes: opioid-related accidents and overdoses, alcohol- and non-opioid drug-related accidents and overdoses, self-inflicted injuries, violence-related injuries, wounds/injuries overall, and death. A logistic propensity score adjusted regression controlling for propensity toward concomitant use was used to determine the association of concomitant use with adverse outcomes. The final matched sample consisted of 396,141 non-acute opioid only using Veterans and 48,971 concomitant benzodiazepine-opioid users. Receiving opioids and benzodiazepines concomitantly increased the risk of experiencing an adverse outcome with an odds ratio of 1.359 (95%CI:1.320-1.400; p<.0001). Among Veterans receiving opioids, concomitant benzodiazepine use is associated with an increased risk of adverse outcomes when compared to the baseline risk of opioid only using Veterans.

CHRONIC PAIN (Continued)

Dangerously numb: Opioids, benzodiazepines, chronic pain, and posttraumatic stress disorder.

Sullivan M[1].

Pain. **2017 Dec 6**. doi: 10.1097/j.pain.0000000000001128. PMID: 29334531. [Epub ahead of print]

Link to full text in Pain for this *Commentary on abstract above*: Gressler LE, Martin BC, Hudson TJ, Painter JT. The relationship between concomitant benzodiazepine-opioid use and adverse outcomes among U.S. veterans. Pain 2017.

The study by Gressler et al. is an important and timely study concerning the risk of adverse outcomes associated with the concurrent prescribing of opioids and benzodiazepines in the entire Veteran patient population between 2008 and 2012. Recent studies have documented an increased risk of overdose death in veterans prescribed both opioids and benzodiazepines. From 2004 to 2009, 27% of veterans receiving opioids also received benzodiazepines. This group accounted for half of overdose deaths during that period. Adjusted risk for death was nearly 4 times higher in the concurrent prescription group, with the risk increasing as the benzodiazepine dose increased. The study by Gressler et al. advances the field through careful attention to confounding by indication. This is important because the patients who receive opioids and benzodiazepines are not the same patients as those who receive only opioids. The differences between these groups must be controlled for in any attempt to quantify the risk associated with the benzodiazepine prescription itself.

This experienced pharmacoepidemiology team has used sophisticated methods to address confounding, including matching cases and controls on a propensity score, and the cohort entry date. The authors nicely document the higher risk opioid prescribing that characterizes the opioid-benzo users (eg, in higher dose and longer duration), which points to the importance of good matching. They focus on the group with at least 20 days of opioids in a 60-day period because the dangers of coprescribing are not limited to the group with long-term (≥90 days) opioid use. Nevertheless, the opioid–benzodiazepine group was more likely to be long-term users of both opioids and benzodiazepines. The investigators' list of adverse outcomes extends beyond fatal overdose to include opioid-related accidents and overdoses, alcohol-related and nonopioid drug–related accidents and overdoses, self-inflicted injuries, violence-related injuries, and wounds/ injuries overall. This gives us a more complete picture of the adverse outcomes of concurrent prescription. After these careful controls, the authors were able to demonstrate a 36% increased risk of adverse outcomes in the opioid–benzodiazapine prescription group. All categories of adverse outcomes (injuries, accidents, overdoses, and deaths) were increased.

Genetic and environmental influences to low back pain and symptoms of depression and anxiety: A population-based twin study.

Pinheiro MB[1], Morosoli JJ[2], Colodro-Conde L[3], Ferreira PH[4], Ordoñana JR[5].

J Psychosom Res. **2018 Feb**;105:92-98. doi: 10.1016/j.jpsychores.2017.12.007. Epub 2017 Dec 6.

BACKGROUND: People suffering from chronic pain are more likely to experience symptoms of depression and anxiety. However, the mechanisms underlying this relationship remain largely unknown. In light of the moderate to large effects of genetic factors on chronic pain and depression and anxiety, we aimed to estimate the relative contribution of genetic and environmental factors to the relationship between these traits.

METHODS: Using data from 2139 participants in the Murcia Twin Registry, we employed a bivariate analysis and structural equation modeling to estimate the relative influences of genetics and the environment on the covariation between low back pain and symptoms of depression and anxiety.

RESULTS: We have obtained heritability estimates of 0.26 (95% Confidence Interval (CI) 0.11, 0.41) for chronic low back pain and 0.45 (95% CI 0.29, 0.50) for symptoms of depression and anxiety. The phenotypic, genetic, and unique environment correlations in the bivariate analytical model were, respectively, r_{ph}=0.26 (95% CI 0.19, 0.33); r_G=0.47 (95% CI 0.42, 0.70); r_E=0.14 (95% CI -0.04, 0.25). The percentage of covariance between low back pain and symptoms of depression and anxiety attributable to additive genetic factors was 63.6%, and to unique environment 36.4%.

CONCLUSIONS: Our findings confirm the relationship between low back pain and symptoms of depression and anxiety in a non-clinical sample. Shared genetic factors affect significantly the covariation between these conditions, supporting the role of common biological and physiological pathways.

CHRONIC PAIN (Continued)

Health literacy, pain intensity and pain perception in patients with chronic pain.

Köppen PJ[1,2], Dorner TE[3], Stein KV[4], Simon J[5], Crevenna R[6].

Wien Klin Wochenschr. **2018 Jan 10**. doi: 10.1007/s00508-017-1309-5. [Epub ahead of print]

BACKGROUND: Chronic pain poses a large burden for the healthcare system and the individuals concerned. The impact of health literacy (HL) on health status and health outcomes is receiving more and more attention. The aim of this study was to evaluate the association of HL with chronic pain intensity and pain perception.

METHODS: A total of 121 outpatients suffering from chronic pain (pain duration >3 months) were evaluated. The HL was measured using the health literacy screening questions. Pain intensity was measured with a Visual Analogue Scale (VAS) and pain perception with the short-form McGill Pain Questionnaire (SF-MPQ).

RESULTS: Individuals with low HL had significantly higher VAS values (Pearson correlation coefficient= -0.270, p = 0.003). Stepwise regression analysis showed that HL has a significant association with pain intensity (odds ratio [OR] = 2.31; 95% confidence interval [CI] 1.11-4.83), even after controlling for age and sex (OR = 2.27; 95% CI 1.07-4.82), but no longer after controlling for education (OR = 2.10; 95% CI 0.95-4.64).

CONCLUSION: Individuals with a higher HL showed less pain intensity, which seems to be caused by a better pain management; therefore, supporting the development of HL in patients with chronic pain could be seen as an important objective of integrated care.

Psychological flexibility mediates the effect of an online-based acceptance and commitment therapy for chronic pain: an investigation of change processes.

Lin J[1,2], Klatt LI[3], McCracken LM[2,4], Baumeister H[5].

Pain. **2017 Dec 15**. doi: 10.1097/j.pain.0000000000001134. [Epub ahead of print]

One way to improve treatment effects of chronic pain is to identify and improve control over mechanisms of therapeutic change. One treatment approach that includes a specific proposed mechanism is acceptance and commitment therapy (ACT) with its focus on increasing psychological flexibility (PF). The aim of the present study was to examine the role of PF as a mechanism of change in ACT. This is based on mediation analyses of data from a previously reported randomized controlled trial, evaluating the effectiveness of an ACT-based online intervention for chronic pain (ACTonPain). We performed secondary analyses on pretreatment, posttreatment, and follow-up data from 302 adults, receiving a guided (n = 100) or unguided (n = 101) version of ACTonPain, or allocated to the waitlist control group (n = 101). Structural equation modelling and a bias-corrected bootstrap approach were applied to examine the indirect effects of the treatment through pretreatment and posttreatment changes in the latent construct reflecting PF. The latent construct consisted of data from the Chronic Pain Acceptance Questionnaire and the Acceptance and Action Questionnaire. The outcomes were pretreatment to follow-up changes in pain interference, anxiety, depression, pain, and mental and physical health. Structural equation modelling analyses revealed that changes in PF significantly mediated pretreatment to follow-up changes in all outcomes in the intervention groups compared with waitlist (standardized estimates ranged from I0.16I to I0.69I). Global model fit yielded modest but acceptable results. Findings are consistent with the theoretical framework behind ACT and contribute to growing evidence, supporting a focus on PF to optimize treatment effects.

OTHER RESEARCH OF INTEREST

Exposure reporting disparity in Gulf War Registry-related clinical assessments.

Metzger-Smith V[1], Lei K[2], Javors J[1], Golshan S[1,2], Leung A[1,2,3].

SAGE Open Med. **2017 Dec 21**;5:2050312117746567. doi: 10.1177/2050312117746567. eCollection 2017. PMCID: PMC5753886.

Objectives: The Gulf War Registry monitors related health conditions of veterans returning from the Persian Gulf Region. Enrollment consists of two phases: Phase I-veterans meet with their local VA Environmental Health Coordinator and complete the self-reported Gulf War Phase I Worksheet (VA Form 10-9009A). Phase II involves a physical exam, medical history review, and laboratory test analysis conducted by a licensed physician. The providers' documentations are frequently referred for exposure assessment and benefit claim. We conducted an initial comparison assessment to ascertain any potential disparity in exposure reporting between the applicants in Phase I and the providers in Phase II.

Methods: With institutional human subject committee approval, a list of veterans with a Gulf War Registry electronic medical note from the VA San Diego Healthcare System (2013-2015) was obtained. Comparing Phase I with Phase II reports allows three distinct reporting group combinations for each of the 21 exposure categories. Group I: both the patients and the healthcare personnel provided the same report for the respective exposure. Group II: healthcare personnel but not the patients reported the exposure. Group III: only the patients but not the healthcare personnel reported the exposure.

Results: A total of 178 (of 367) subjects had both the medical note from the healthcare provider and a physical copy of their Phase I Worksheet available, and therefore were eligible to be included in the overall one-way and subsequent pair-wise chi-square analyses. The results indicate that Group I reporting pattern had a significantly ($p < 0.01$) lower prevalence in nine exposure categories compared to Group III.

Conclusion: The findings suggest that the medical documentation from the healthcare providers does not consistently and accurately reflect the patients' report in near 50% (9/21) of assessed exposure categories. Potential remedies addressing this exposure reporting disparity, such as a standardized template or electronic upload, are further discussed.

National Prevalence and Effects of Multiple Chemical Sensitivities.

Steinemann A[1].

J Occup Environ Med. **2018 Jan 11**. doi: 10.1097/JOM.0000000000001272. [Epub ahead of print]

OBJECTIVE: To assess the prevalence of multiple chemical sensitivities (MCS), its co-occurrence with asthma and fragrance sensitivity, and effects from exposure to fragranced consumer products.

METHODS: A nationally representative cross-sectional population-based sample of adult Americans (n=1,137) was surveyed in June 2016.

RESULTS: Among the population, 12.8% report medically diagnosed MCS and 25.9% report chemical sensitivity. Of those with MCS, 86.2% experience health problems, such as migraine headaches, when exposed to fragranced consumer products; 71.0% are asthmatic; 70.3% cannot access places that use fragranced products such as air fresheners; and 60.7% lost workdays or a job in the past year due to fragranced products in the workplace.

CONCLUSIONS: Prevalence of diagnosed MCS has increased over 300%, and self-reported chemical sensitivity over 200%, in the past decade. Reducing exposure to fragranced products could help reduce adverse health and societal effects.

OTHER RESEARCH OF INTEREST (Continued)

Controlled Low-Pressure Blast-Wave Exposure Causes Distinct Behavioral and Morphological Responses Modelling Mild Traumatic Brain Injury, Post-Traumatic Stress Disorder, and Comorbid Mild Traumatic Brain Injury-Post-Traumatic Stress Disorder.

Zuckerman A[1], Ram O[2], Ifergane G[3], Matar MA[1], Sagi R[4], Ostfeld I[4], Hoffman JR[5], Kaplan Z[1], Sadot O[2], Cohen H[1].

J Neurotrauma. **2017 Jan 1**;34(1):145-164. doi: 10.1089/neu.2015.4310. Epub 2016 Mar 30.

The intense focus in the clinical literature on the mental and neurocognitive sequelae of explosive blast-wave exposure, especially when comorbid with post-traumatic stress-related disorders (PTSD) is justified, and warrants the design of translationally valid animal studies to provide valid complementary basic data. We employed a controlled experimental blast-wave paradigm in which unanesthetized animals were exposed to visual, auditory, olfactory, and tactile effects of an explosive blast-wave produced by exploding a thin copper wire. By combining cognitive-behavioral paradigms and ex vivo brain MRI to assess mild traumatic brain injury (mTBI) phenotype with a validated behavioral model for PTSD, complemented by morphological assessments, this study sought to examine our ability to evaluate the biobehavioral effects of low-intensity blast overpressure on rats, in a translationally valid manner. There were no significant differences between blast- and sham-exposed rats on motor coordination and strength, or sensory function. Whereas most male rats exposed to the blast-wave displayed normal behavioral and cognitive responses, 23.6% of the rats displayed a significant retardation of spatial learning acquisition, fulfilling criteria for mTBI-like responses. In addition, 5.4% of the blast-exposed animals displayed an extreme response in the behavioral tasks used to define PTSD-like criteria, whereas 10.9% of the rats developed both long-lasting and progressively worsening behavioral and cognitive "symptoms," suggesting comorbid PTSD-mTBI-like behavioral and cognitive response patterns. Neither group displayed changes on MRI. Exposure to experimental blast-wave elicited distinct behavioral and morphological responses modelling mTBI-like, PTSD-like, and comorbid mTBI-PTSD-like responses. This experimental animal model can be a useful tool for elucidating neurobiological mechanisms underlying the effects of blast-wave-induced mTBI and PTSD and comorbid mTBI-PTSD.

Morris MC[1], Wang Y[2], Barnes LL[2], Bennett DA[2], Dawson-Hughes B[2], Booth SL[2].

Neurology. **2017 Dec 20**. pii: 10.1212/WNL.0000000000004815. PMID: 29263222. [Epub ahead of print]

OBJECTIVE: To increase understanding of the biological mechanisms underlying the association, we investigated the individual relations to cognitive decline of the primary nutrients and bioactives in green leafy vegetables, including vitamin K (phylloquinone), lutein, β-carotene, nitrate, folate, kaempferol, and α-tocopherol.

METHODS: This was a prospective study of 960 participants of the Memory and Aging Project, ages 58-99 years, who completed a food frequency questionnaire and had ≥2 cognitive assessments over a mean 4.7 years.

RESULTS: In a linear mixed model adjusted for age, sex, education, participation in cognitive activities, physical activities, smoking, and seafood and alcohol consumption, consumption of green leafy vegetables was associated with slower cognitive decline; the decline rate for those in the highest quintile of intake (median 1.3 servings/d) was slower by β = 0.05 standardized units (p = 0.0001) or the equivalent of being 11 years younger in age. Higher intakes of each of the nutrients and bioactives except β-carotene were individually associated with slower cognitive decline. In the adjusted models, the rates for the highest vs the lowest quintiles of intake were β = 0.02, p = 0.002 for phylloquinone; β = 0.04, p = 0.002 for lutein; β = 0.05, p < 0.001 for folate; β = 0.03, p = 0.02 for α-tocopherol; β = 0.04, p = 0.002 for nitrate; β = 0.04, p = 0.003 for kaempferol; and β = 0.02, p = 0.08 for β-carotene.

CONCLUSIONS: Consumption of approximately 1 serving per day of green leafy vegetables and foods rich in phylloquinone, lutein, nitrate, folate, α-tocopherol, and kaempferol may help to slow cognitive decline with aging.

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