

## GULF WAR ILLNESS

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

## CHRONIC FATIGUE SYNDROME

### [Prediction of long-term outcome after cognitive behavioral therapy for chronic fatigue syndrome.](#)

[Janse A](#)<sup>1</sup>, [Bleijenberg G](#)<sup>2</sup>, [Knoop H](#)<sup>3</sup>.

J Psychosom Res. **2019 Jun**;121:93-99. doi: 10.1016/j.jpsychores.2019.03.017. PMID: 31006534. Epub 2019 Mar 19.

**OBJECTIVE:** To determine which variables predicted long-term outcome after cognitive behavioral therapy (CBT) for chronic fatigue syndrome (CFS).

**METHODS:** A cohort of 511 CFS patients from four different CBT for CFS studies, i.e. two cohort studies and two RCT's. Before treatment, all patients fulfilled the 2003 US CDC criteria for CFS and treated with CBT, were assessed at long-term follow-up, up to 10 years after end of treatment. We tried to predict fatigue severity and physical functioning at follow-up with demographics, cognitive-behavioral perpetuating factors, and CFS characteristics as predictors in linear regression analyses. Logistic regression analysis was used to explore significant predictors of fatigue scores within normal limits at long-term follow-up.

**RESULTS:** Lower fatigue severity at long-term follow-up was predicted by a shorter duration of CFS symptoms and lower fatigue levels at baseline, and lower frustration in response to fatigue and lower fatigue levels directly post-treatment. Fatigue scores within normal limits at follow-up was predicted by lower fatigue severity and lower levels of frustration in response to fatigue, both assessed directly post-treatment. Better physical functioning at follow-up was predicted by higher sense of control over fatigue, better physical functioning at post-treatment, and being younger at baseline. In some of the additional analysis pain at baseline also predicted physical functioning at follow-up.

**CONCLUSION:** The finding that lower fatigue severity and higher physical functioning at long-term follow-up were positively associated with its outcomes at post-treatment underline the importance of fully maximizing the positive effects of CBT for the sustainment of outcomes. Furthermore, augmenting sense of control and starting treatment sooner after diagnosing CFS could positively influence long-term outcome. Interventions aimed at pain management deserve more attention in research.

## HEADACHE and MIGRAINE

### [Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis.](#)

[Goadsby PJ](#)<sup>1</sup>, [Dodick DW](#)<sup>2</sup>, [Martinez JM](#)<sup>3</sup>, [Ferguson MB](#)<sup>3</sup>, [Oakes TM](#)<sup>3</sup>, [Zhang Q](#)<sup>4</sup>, [Skljarevski V](#)<sup>3</sup>, [Aurora SK](#)<sup>3</sup>.

J Neurol Neurosurg Psychiatry. **2019 Aug**;90(8):939-944. doi: 10.1136/jnnp-2018-320242. PMID: 31004075. Epub 2019 Apr 19.

**BACKGROUND AND OBJECTIVE:** As new migraine prevention treatments are developed, the onset of a preventive effect, how long it is maintained and whether patients initially non-responsive develop clinically meaningful responses with continued treatment can be assessed.

**METHODS:** Analyses were conducted post-hoc of a double-blind, placebo-controlled, phase II-a study in patients with episodic migraine receiving galcanezumab 150 mg or placebo biweekly for 12 weeks (*Lancet Neurol* 13:885, 2014). The number of migraine headache days per week, and onset of efficacy measured as the first week galcanezumab separated from placebo were determined. Patients with  $\geq 50\%$ ,  $\geq 75\%$  and 100% reduction in migraine headache days from baseline at months 1, 2 and 3 were calculated and defined as sustained responses. Non-responders ( $< 50\%$  response) at month 1 or 2 who then showed  $\geq 50\%$ ,  $\geq 75\%$  and 100% response at later time-points were calculated.

**RESULTS:** Patients were randomised to galcanezumab (n=107) or placebo (n=110). A significant (p=0.018) change of  $-0.89 \pm 0.11$  (galcanezumab) vs  $-0.53 \pm 0.11$  (placebo) migraine headache days indicated onset at week 1. Forty-seven per cent of galcanezumab and 25% of placebo patients responding at month 1 maintained response through months 2 and 3. Of non-responders at month 1, 27% on galcanezumab and 20% on placebo responded on months 2 and 3, and 50% of galcanezumab non-responders in months 1 and 2 responded on month 3, vs 24% on placebo.

**CONCLUSIONS:** The onset of efficacy of galcanezumab is within 1 week in a majority of patients, and patients receiving galcanezumab are twice more likely to maintain responses than placebo patients. Early non-responders may respond by month 2 or month 3.

TRIAL REGISTRATION NUMBER: [NCT01625988](#).

## CHRONIC PAIN

### [Chronic pain is associated with a brain aging biomarker in community-dwelling older adults.](#)

[Cruz-Almeida Y](#)<sup>1,2,3,4,5</sup>, [Fillingim RB](#)<sup>1,2</sup>, [Riley JL 3rd](#)<sup>1,2</sup>, [Woods AJ](#)<sup>3,5,6</sup>, [Porges E](#)<sup>3,6</sup>, [Cohen R](#)<sup>3,6</sup>, [Cole J](#)<sup>7</sup>.

Pain. **2019 May**;160(5):1119-1130. doi: 10.1097/j.pain.0000000000001491. PMID: 31009418.

Chronic pain is associated with brain atrophy with limited evidence on its impact in the older adult's brain. We aimed to determine the associations between chronic pain and a brain aging biomarker in persons aged 60 to 83 years old. Participants of the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) study (N = 47) completed demographic, psychological, and pain assessments followed by a quantitative sensory testing battery and a T1-weighted magnetic resonance imaging. We estimated a brain-predicted age difference (brain-PAD) that has been previously reported to predict overall mortality risk (brain-PAD, calculated as brain-predicted age minus chronological age), using an established machine-learning model. Analyses of covariances and Pearson/Spearman correlations were used to determine associations of brain-PAD with pain, somatosensory function, and psychological function. Individuals with chronic pain (n = 33) had "older" brains for their age compared with those without (n = 14;  $F[1,41] = 4.9$ ;  $P = 0.033$ ). Greater average worst pain intensity was associated with an "older" brain ( $r = 0.464$ ;  $P = 0.011$ ). Among participants with chronic pain, those who reported having pain treatments during the past 3 months had "younger" brains compared with those who did not ( $F[1,27] = 12.3$ ;  $P = 0.002$ ). An "older" brain was significantly associated with decreased vibratory ( $r = 0.323$ ;  $P = 0.033$ ) and thermal ( $r = 0.345$ ;  $P = 0.023$ ) detection, deficient endogenous pain inhibition ( $F[1,25] = 4.6$ ;  $P = 0.044$ ), lower positive affect ( $r = -0.474$ ;  $P = 0.005$ ), a less agreeable ( $r = -0.439$ ;  $P = 0.020$ ), and less emotionally stable personality ( $r = -0.387$ ;  $P = 0.042$ ). Our findings suggest that chronic pain is associated with added "age-like" brain atrophy in relatively healthy, community-dwelling older individuals, and future studies are needed to determine the directionality of our findings. A brain aging biomarker may help identify people with chronic pain at a greater risk of functional decline and poorer health outcomes.

### [Adverse Childhood Experiences in Mothers With Chronic Pain and Intergenerational Impact on Children.](#)

[Dennis CH](#)<sup>1</sup>, [Clohessy DS](#)<sup>2</sup>, [Stone AL](#)<sup>3</sup>, [Darnall BD](#)<sup>4</sup>, [Wilson AC](#)<sup>3</sup>.

J Pain. **2019 Apr 18**. pii: S1526-5900(18)30525-X. doi: 10.1016/j.jpain.2019.04.004. PMID: 31005595. [Epub ahead of print]

Adverse childhood experiences (ACEs; eg, parental divorce, physical or sexual abuse) are more prevalent in individuals with chronic pain compared with the general population. Both increased maternal ACEs and chronic pain have been associated with poor physical and emotional functioning in offspring. However, the mechanisms driving these associations are poorly understood. Thus, this cross-sectional study evaluated the relation between maternal ACEs, mothers' current functioning, and children's physical and emotional functioning in a sample of mothers with chronic pain and their 8- to 12-year-old children. Results indicated a higher prevalence of  $\geq 1$  ACE in this sample of mothers with chronic pain (84%) compared with normative data from a community sample of women. Higher maternal ACE scores corresponded with lower physical and social functioning, greater anxiety and depressive symptoms, greater fatigue and sleep disturbances, and greater pain intensity and pain interference in mothers. Higher maternal ACE scores significantly correlated with higher child self-reported depressive symptoms, but not somatic symptoms or functional impairment. A path model indicated that maternal depressive symptoms accounted for the relation between higher maternal ACE scores and children's depressive symptoms. Intervening on maternal depression among mothers with chronic pain may reduce the impact of intergenerational ACE transmission. Perspective: This article presents evidence regarding the intergenerational impact of ACEs in a large sample of mothers with chronic pain and their school-aged children. Maternal depressive symptoms accounted for the relation between maternal ACEs and children's depressive symptoms providing evidence regarding targets for preventive interventions.

## IRRITABLE BOWEL SYNDROME

### [Glutamatergic Signaling Along The Microbiota-Gut-Brain Axis.](#)

[Baj A](#)<sup>1</sup>, [Moro E](#)<sup>2</sup>, [Bistoletti M](#)<sup>3</sup>, [Orlandi V](#)<sup>4</sup>, [Crema F](#)<sup>5</sup>, [Giaroni C](#)<sup>6</sup>.

Int J Mol Sci. **2019 Mar 25**;20(6). pii: E1482. doi: 10.3390/ijms20061482. PMCID: PMC6471396. PMID: 30934533.

A complex bidirectional communication system exists between the gastrointestinal tract and the brain. Initially termed the "gut-brain axis" it is now renamed the "microbiota-gut-brain axis" considering the pivotal role of gut microbiota in maintaining local and systemic homeostasis. Different cellular and molecular pathways act along this axis and strong attention is paid to neuroactive molecules (neurotransmitters, i.e., noradrenaline, dopamine, serotonin, gamma aminobutyric acid and glutamate and metabolites, i.e., tryptophan metabolites), sustaining a possible interkingdom communication system between eukaryota and prokaryota. This review provides a description of the most up-to-date evidence on glutamate as a neurotransmitter/neuromodulator in this bidirectional communication axis. Modulation of glutamatergic receptor activity along the microbiota-gut-brain axis may influence gut (i.e., taste, visceral sensitivity and motility) and brain functions (stress response, mood and behavior) and alterations of glutamatergic transmission may participate to the pathogenesis of local and brain disorders. In this latter context, we will focus on two major gut disorders, such as irritable bowel syndrome and inflammatory bowel disease, both characterized by psychiatric co-morbidity. Research in this area opens the possibility to target glutamatergic neurotransmission, either pharmacologically or by the use of probiotics producing neuroactive molecules, as a therapeutic approach for the treatment of gastrointestinal and related psychiatric disorders.

### [Gut \*Prevotella\* as a possible biomarker of diet and its eubiotic versus dysbiotic roles: A comprehensive literature review.](#)

[Precup G](#)<sup>1</sup>, [Vodnar DC](#)<sup>1</sup>.

Br J Nutr. **2019 Mar 29**:1-24. doi: 10.1017/S0007114519000680. PMID: 30924428. [Epub ahead of print]

Gut microbiota has a profound impact on human health. Emerging data shows that dietary patterns are associated with different communities of bacterial species within the gut. *Prevotella* species have been correlated with plant rich diets, abundant in carbohydrates and fibres. Dysbiosis within the gut ecosystem has been associated with the development of non-communicable diseases such as obesity, metabolic syndrome, inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, type 1 diabetes, allergies and other diseases. The purpose of this comprehensive literature review was to evaluate the available data on the impact of diet on *Prevotella* genus, as a dietary fibre fermenter in the gut, as well as its implications as a potential biomarker for homeostasis or disease state, through its metabolite signature. Studies were identified by conducting PubMed, Web of Science Core Collection and Google Scholar electronic searches. We found 85 publications reporting the impact of dietary patterns on gut microbial communities including *Prevotella* or *Prevotella/Bacteroides* ratio in particular. Moreover, the role of *Prevotella* species on health status was also evaluated. *Prevotella* possess a high genetic diversity, representing one of the important groups found in the oral cavity and large intestine of man. The gut commensal *Prevotella* bacteria contribute to polysaccharide breakdown, being dominant colonizers of agrarian societies. However, studies also suggested a potential role of *Prevotella* species as intestinal pathobionts. Further metagenomic studies are needed in order to reveal health- or disease-modulating properties of *Prevotella* species in the gut.

## OTHER RESEARCH OF INTEREST

### [FDA approves first generic naloxone nasal spray to treat opioid overdose](#)

*Agency is also taking new steps to support development of over-the-counter and additional generics of naloxone to help reduce opioid overdose deaths, increase access to emergency treatment*

FDA News Release: **April 19, 2019**

The U.S. Food and Drug Administration today granted final approval of the first generic naloxone hydrochloride nasal spray, commonly known as Narcan, a life-saving medication that can stop or reverse the effects of an opioid overdose. The agency is also planning new steps to prioritize the review of additional generic drug applications for products intended to treat opioid overdose, along with the previously announced action to help facilitate an [over-the-counter naloxone product](#).

“In the wake of the opioid crisis, a number of efforts are underway to make this emergency overdose reversal treatment more readily available and more accessible. In addition to this approval of the first generic naloxone nasal spray, moving forward we will prioritize our review of generic drug applications for naloxone. The FDA has also taken the unprecedented step of helping to assist manufacturers to pursue approval of an over-the-counter naloxone product and is exploring other ways to increase the availability of naloxone products intended for use in the community, including whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death,” said Douglas Throckmorton, M.D., deputy center director for regulatory programs in the FDA’s Center for Drug Evaluation and Research. “All together, these efforts have the potential to put a vital tool for combatting opioid overdose in the hands of those who need it most – friends and families of opioid users, as well as first responders and community-based organizations. We’re taking many steps to improve availability of naloxone products, and we’re committed to working with other federal, state and local officials as well as health care providers, patients and communities across the country to combat the staggering human and economic toll created by opioid abuse and addiction.”

Today’s approval is the first generic naloxone nasal spray for use in a community setting by individuals without medical training; however, generic injectable naloxone products have been available for years for use in a health care setting. The FDA also has previously approved a brand-name naloxone nasal spray and an auto-injector for use by those without medical training. While business and other considerations may impact how quickly this product becomes available, today’s approval is an important step for the agency as it works toward expanding access to this life-saving drug. The FDA also held a [two-day advisory committee](#) meeting in December to solicit input and advice on strategies to increase the availability of naloxone products intended for use in the community.

According to the [Centers for Disease Control and Prevention](#), almost 400,000 people died from an opioid overdose from 1999 to 2017, and on average, more than 130 Americans die every day from overdoses involving opioids, a class of drugs that include prescription medications such as fentanyl, oxycodone, hydrocodone and morphine, as well as illegal drugs such as heroin or drugs sold as heroin. Drugs like heroin often contain fentanyl or derivatives of fentanyl. When someone overdoses on an opioid, it can be difficult to revive the person to full consciousness, and breathing may become shallow or stop completely – leading to death without medical intervention. If [naloxone nasal spray](#) is administered quickly, it can counter the overdose effects, usually within minutes. However, it is important to note that it is not a substitute for immediate medical care, and the person administering naloxone nasal spray should seek further immediate medical attention on the patient’s behalf.

As part of the U.S. Department of Health and Human Services’ ongoing efforts to combat the opioid crisis and expand the use of naloxone, in April 2017, the Department announced its [5-Point Strategy](#) to Combat the Opioids Crisis. Those efforts include: better addiction prevention, treatment, and recovery services; better data; better pain management; better targeting of overdose reversing drugs; and better research. In April 2018, Surgeon General VADM Jerome Adams issued an [advisory](#) encouraging more individuals, including family, friends and those who are personally at risk for an opioid overdose to carry naloxone. In December 2018, ADM Brett P. Giroir, M.D., Assistant Secretary for Health and the Secretary’s Senior Advisor for Opioid Policy, released [guidance](#) for health care providers and patients detailing how naloxone can help save lives....

[Full Text continues at [FDA News Release](#).]

## OTHER RESEARCH OF INTEREST (Continued)

**Residual symptoms following prolonged exposure and present-centered therapy for PTSD in female veterans and soldiers.**Schnurr PP<sup>1,2</sup>, Lunney CA<sup>1</sup>.Depress Anxiety. **2019 Feb**;36(2):162-169. doi: 10.1002/da.22871. PMID: 30576030. Epub 2018 Dec 21.

**BACKGROUND:** Despite the effectiveness of evidence-based treatments for posttraumatic stress disorder (PTSD), some symptoms, such as sleep disturbance, can be difficult to treat regardless of treatment type.

**METHODS:** We examined residual PTSD symptoms in 235 female veterans and soldiers who were randomized to receive 10 weekly sessions of either Prolonged Exposure (PE) or Present-Centered Therapy (PCT). PTSD symptoms were assessed using the Clinician-Administered PTSD Scale. Analyses examined the effects of PE and the effects of clinically significant improvement (loss of diagnosis, operationalized as meaningful symptom reduction and no longer meeting diagnostic criteria).

**RESULTS:** Both treatments resulted in reductions in PTSD symptoms. PE had lower conditional probabilities than PCT of retaining intrusive memories, avoidance of people/places, detachment/estrangement, and restricted range of affect. Loss of diagnosis had lower conditional probabilities of almost all symptoms, although hyperarousal symptoms—especially irritability/anger (60.7%) and sleep difficulties (50.9%)—were the most likely to remain.

**CONCLUSIONS:** Results are consistent with previous findings on sleep difficulties being difficult to treat, but also show that hyperarousal symptoms overall may not be resolved even after substantial improvement. Additional strategies may be needed to treat the full range of PTSD symptoms in some patients.

**TRIAL REGISTRATION:** ClinicalTrials.gov [NCT00032617](https://clinicaltrials.gov/ct2/show/study/NCT00032617).

**Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults With Depression: A Network Meta-analysis.**Cuijpers P<sup>1</sup>, Noma H<sup>2</sup>, Karyotaki E<sup>2</sup>, Cipriani A<sup>3,4</sup>, Furukawa TA<sup>5</sup>.JAMA Psychiatry. **2019 Apr 17**. doi: 10.1001/jamapsychiatry.2019.0268. PMID: 30994877. [Epub ahead of print]

**Importance:** Cognitive behavior therapy (CBT) has been shown to be effective in the treatment of acute depression. However, whether CBT can be effectively delivered in individual, group, telephone-administered, guided self-help, and unguided self-help formats remains unclear.

**Objective:** To examine the most effective delivery format for CBT via a network meta-analysis.

**Data Sources:** A database updated yearly from PubMed, PsycINFO, Embase, and the Cochrane Library. Literature search dates encompassed January 1, 1966, to January 1, 2018.

**Study Selection:** Randomized clinical trials of CBT for adult depression. The 5 treatment formats were compared with each other and the control conditions (waiting list, care as usual, and pill placebo).

**Data Extraction and Synthesis:** PRISMA guidelines were used when extracting data and assessing data quality. Data were pooled using a random-effects model. Pairwise and network meta-analyses were conducted.

**Main Outcomes and Measures:** Severity of depression and acceptability of the treatment formats.

**Results:** A total of 155 trials with 15 191 participants compared 5 CBT delivery formats with 2 control conditions. In half of the studies (78 [50.3%]), patients met the criteria for a depressive disorder; in the other half (77 [49.7%]), participants scored above the cutoff point on a self-report measure. The effectiveness of individual, group, telephone, and guided self-help CBT did not differ statistically significantly from each other. These formats were statistically significantly more effective than the waiting list (standardized mean differences [SMDs], 0.87-1.02) and care as usual (SMDs, 0.47-0.72) control conditions as well as the unguided self-help CBT (SMDs, 0.34-0.59). In terms of acceptability (dropout for any reason), individual (relative risk [RR] = 1.44; 95% CI, 1.09-1.89) and group (RR = 1.38; 95% CI, 1.06-1.80) CBT were significantly better than guided self-help. Guided self-help was also less acceptable than being on a waiting list (RR = 0.63; 95% CI, 0.52-0.75) and care as usual (RR = 0.72; 95% CI, 0.57-0.90). Sensitivity analyses supported the overall findings.

**Conclusions and Relevance:** For acute symptoms of depression, group, telephone, and guided self-help treatment formats appeared to be effective interventions, which may be considered as alternatives to individual CBT; although there were few indications of significant differences in efficacy between treatments with human support, guided self-help CBT may be less acceptable for patients than individual, group, or telephone formats.

## OTHER RESEARCH OF INTEREST (Continued)

**Screening for Breast Cancer in Average-Risk Women: A Guidance Statement From the American College of Physicians.**

[Qaseem A](#)<sup>1</sup>, [Lin JS](#)<sup>2</sup>, [Mustafa RA](#)<sup>3</sup>, [Horwitch CA](#)<sup>4</sup>, [Wilt TJ](#)<sup>5</sup>; [Clinical Guidelines Committee of the American College of Physicians.](#)

Ann Intern Med. 2019 Apr 9. doi: 10.7326/M18-2147. PMID: 30959525. [Epub ahead of print]

**Description:** The purpose of this guidance statement is to provide advice to clinicians on breast cancer screening in average-risk women based on a review of existing guidelines and the evidence they include.

**Methods:** This guidance statement is derived from an appraisal of selected guidelines from around the world that address breast cancer screening, as well as their included evidence. All national guidelines published in English between 1 January 2013 and 15 November 2017 in the National Guideline Clearinghouse or Guidelines International Network library were included. In addition, the authors selected other guidelines commonly used in clinical practice. Web sites associated with all selected guidelines were checked for updates on 10 December 2018. The AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument was used to evaluate the quality of guidelines.

**Target Audience and Patient Population:** The target audience is all clinicians, and the target patient population is all asymptomatic women with average risk for breast cancer.

**Guidance Statement 1:** In average-risk women aged 40 to 49 years, clinicians should discuss whether to screen for breast cancer with mammography before age 50 years. Discussion should include the potential benefits and harms and a woman's preferences. The potential harms outweigh the benefits in most women aged 40 to 49 years.

**Guidance Statement 2:** In average-risk women aged 50 to 74 years, clinicians should offer screening for breast cancer with biennial mammography.

**Guidance Statement 3:** In average-risk women aged 75 years or older or in women with a life expectancy of 10 years or less, clinicians should discontinue screening for breast cancer.

**Guidance Statement 4:** In average-risk women of all ages, clinicians should not use clinical breast examination to screen for breast cancer.

**Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults: A Cohort Study.**

[Chen F](#)<sup>1</sup>, [Du M](#)<sup>2</sup>, [Blumberg JB](#)<sup>2</sup>, [Ho Chui KK](#)<sup>3</sup>, [Ruan M](#)<sup>4</sup>, [Rogers G](#)<sup>5</sup>, [Shan Z](#)<sup>6</sup>, [Zeng L](#)<sup>2</sup>, [Zhang FF](#)<sup>2</sup>.

Ann Intern Med. 2019 Apr 9. doi: 10.7326/M18-2478. PMID: 30959527. [Epub ahead of print]

**Background:** The health benefits and risks of dietary supplement use are controversial.

**Objective:** To evaluate the association among dietary supplement use, levels of nutrient intake from foods and supplements, and mortality among U.S. adults.

**Design:** Prospective cohort study.

**Setting:** NHANES (National Health and Nutrition Examination Survey) data from 1999 to 2010, linked to National Death Index mortality data.

**Participants:** 30 899 U.S. adults aged 20 years or older who answered questions on dietary supplement use.

**Measurements:** Dietary supplement use in the previous 30 days and nutrient intake from foods and supplements. Outcomes included mortality from all causes, cardiovascular disease (CVD), and cancer.

**Results:** During a median follow-up of 6.1 years, 3613 deaths occurred, including 945 CVD deaths and 805 cancer deaths. Ever-use of dietary supplements was not associated with mortality outcomes. Adequate intake (at or above the Estimated Average Requirement or the Adequate Intake level) of vitamin A, vitamin K, magnesium, zinc, and copper was associated with reduced all-cause or CVD mortality, but the associations were restricted to nutrient intake from foods. Excess intake of calcium was associated with increased risk for cancer death (above vs. at or below the Tolerable Upper Intake Level: multivariable-adjusted rate ratio, 1.62 [95% CI, 1.07 to 2.45]; multivariable-adjusted rate difference, 1.7 [CI, -0.1 to 3.5] deaths per 1000 person-years), and the association seemed to be related to calcium intake from supplements ( $\geq 1000$  mg/d vs. no use: multivariable-adjusted rate ratio, 1.53 [CI, 1.04 to 2.25]; multivariable-adjusted rate difference, 1.5 [CI, -0.1 to 3.1] deaths per 1000 person-years) rather than foods.

**Limitations:** Results from observational data may be affected by residual confounding. Reporting of dietary supplement use is subject to recall bias.

**Conclusion:** Use of dietary supplements is not associated with mortality benefits among U.S. adults.

**Primary Funding Source:** National Institutes of Health.

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