



## May 2022 Study Summaries #Dietitians #SportsNutrition

## **Table of Contents**



Autoimmune Disease & Allergies 2 Studies



**Cognition & Memory** 5 Studies



**Diets & Foods** 4 Studies



Fat Loss 3 Studies



Healthy Aging & Longevity 3 Studies



Immunity & Infectious Disease 2 Studies



Liver Health 6 Studies

1 Studies



Pain, Joints & Bones 1 Studies



Men's Health & Testosterone





Cancer 2 Studies



**Diabetes & Blood Sugar** 3 Studies



**Editor's Picks** 2 Studies



**Gut Health** 1 Studies



**Herbal Supplements** 2 Studies



Infants, Children & Teenagers 3 Studies



Low-Carb & Keto 2 Studies



Muscle Gain & Exercise 7 Studies



Skin, Hair & Aesthetics 1 Studies



## **P** Autoimmune Disease & Allergies

#### Vitamin D and the incidence and severity of atopic dermatitis 2

This meta-analysis found that (i) participants with atopic dermatitis had lower vitamin D levels compared to healthy controls, (ii) participants with severe atopic dermatitis had lower vitamin D levels compared to those with mild or moderate atopic dermatitis, and (iii) vitamin D supplementation improved atopic dermatitis severity.

#### Background

Although observational research suggests that there is a link between vitamin D status and different skin conditions, it's unclear whether vitamin D deficiency is associated with the incidence and severity of *atopic dermatitis* (AD; an inflammatory skin condition) and whether supplementation with vitamin D can improve the severity of AD.

#### The study

This meta-analysis of 20 studies (16 observational and 4 interventional) looked at the following:

- Serum vitamin D levels in participants with AD compared to healthy control participants in 14 observational studies
- Serum vitamin D levels in participants with severe AD compared to those with mild or moderate AD in 11 observational studies
- The effect of vitamin D supplementation on the severity of AD in 4 interventional studies

#### The results

Compared to healthy controls, participants with AD had serum vitamin D levels that were 7.4 ng/mL lower, on average. Participants with severe AD had average serum vitamin D levels that were 10 ng/mL lower than those with mild AD and 3 ng/mL lower than those with moderate AD.

In the analysis of interventional studies, vitamin D supplementation at an average daily dose of approximately 1,700 IU for approximately 3 months improved AD severity, with an average reduction of 11.5 points in the SCORAD severity index.

#### Note

The SCORAD score ranges from 0 to 103 points and defines three classes of AD severity: mild (SCORAD of <25), moderate (SCORAD of 25–50), and severe (SCORAD of >50).

#### **#Dietitians**

#### Omega-3 supplementation for lupus 🛛

This systematic review found some evidence that omega-3 fatty acid supplementation may improve disease activity, clinical features, endothelial function, and inflammatory biomarkers in people with lupus.

#### Background

*Systemic lupus erythematosus* (SLE), also known as lupus, is an autoimmune inflammatory disease characterized by symptoms such as fatigue, joint and muscle pain, and skin lesions and rashes. Omega-3 fatty acids have anti-inflammatory properties; does omega-3 supplementation benefit patients with SLE?

#### The study

This systematic review assessed the efficacy of omega-3 fatty acids on SLE-associated outcomes. The authors included 13 studies (11 interventional clinical trials, 1 survey-based case-control study, and 1 cross-sectional cohort study).

#### The results

**Disease activity**: Of the 11 studies assessing disease activity, 9 reported a beneficial effect of omega-3s.

**Specific clinical features**: Four studies reported improvements in clinical features (constitutional symptoms, energy/fatigue, emotional well-being, sleep disturbances, and components related to the integumentary, neuromuscular, and musculoskeletal systems).

**Biomarkers:** One of 2 studies assessing erythrocyte sedimentation rate reported a reduction following omega-3 supplementation, 1 study reported a decrease in CRP levels, and 1 study reported a reduction in urinary 8-isoprostane (a biomarker of oxidative stress) following fish oil supplementation. In contrast, there were no effects of omega-3s on complement 3 or complement 4 proteins, IgM, IgG (all markers of immune function), or double-stranded dsDNA antibodies (a marker used in diagnosis of lupus).

Kidney parameters: Omega-3s did not affect serum creatinine, urinary IgG, or 24-hour urinary protein.

**Endothelial function**: One of 2 studies assessing red blood cell membrane flexibility and whole blood viscosity reported improvements in both markers. Similarly, 1 of 2 studies assessing flow-mediated dilation reported an improvement following fish oil supplementation.

#### #Dietitians

▲ Back to Table of Contents

# Does daily supplementation with multivitamins and multiminerals reduce the risk of cancer and cardiovascular disease? 🗷

In this randomized controlled trial with a median follow-up period of 3.6 years, daily supplementation with multivitamins and multiminerals did not affect cancer or cardiovascular disease risk.

#### Background

*Multivitamin-multimineral* (MVM) supplements lack a universal definition but typically provide at least 100% of the recommended daily value of most essential vitamins and minerals. They are the most common dietary supplement taken in the U.S.<sup>[100]</sup> Many people take MVM supplements for general health and well-being or to reduce the risk of chronic diseases, but there is a lack of evidence to support their use for the latter effect.

#### The study

This randomized controlled trial examined the effect of a daily MVM supplement use on the incidence of cancer and *cardiovascular disease* (CVD) in 10,723 U.S. adults (average age of 72) free of CVD and *recently diagnosed* cancer over a median follow-up period of 3.6 years. To be included in the study, the participants agreed to forgo personal MVM supplement use and limit supplemental vitamin D and calcium to no more than 1,000 IU/day and no more than 1,200 mg/day during the trial. They also had to complete a placebo run-in phase of at least two months.

## Nutrition label for the multivitamin used in the study

Supplement Facts Serving Size: 1 Tablet		Amount Per Serving	% DV	Amount Per Serving	% DV	Amount Per Serving	% DV
		Thiamin 1.5 mg	125%	Calcium 220 mg	17%	Molybdenum 45 mcg	100%
Amount Per Serving	% DV	Riboflavin 1.7 mg	131%	Phosphorus 20 mg	2%	Chloride 72 mg	3%
Vitamin A 750 mcg (40% as Beta-Carotene)	83%	Niacin 20 mg	125%	lodine 150 mcg	100%	Potassium 80 mg	2%
	0370	Vitamin B <sub>a</sub> 3 mg	176%	Magnesium 50 mg	12%	Lutain 250 mcg	*
		Folate 667 mcg DFE	167%	Zinc 11 mg	100%	Lutein 250 mcg	
Vitamin C 60 mg	min C 60 mg 67%			Selenium 19 mcg	35%	Lycopene 300 mcg	*
Vitamin D <sub>3</sub> 25 mcg (1,000 IU)	125%	Vitamin B, 25 mg	1,042%	Copper 0.5 mg	56%	* Daily Value (DV) not establis	shed.
Vitamin E 22.5 mg	150%	Biotin 30 mcg	100%	Manganese 2.3 mg	100%	2 . /	
Vitamin K 30 mcg	25%	Pantothenic Acid 10 mg	200%	Chromium 50 mcg	143%		

The primary outcome was total invasive cancer, excluding nonmelanoma skin cancer. The secondary outcomes included site-specific cancers (i.e., melanoma, breast cancer, colorectal cancer, lung cancer, and prostate cancer), all-cause mortality, individual cardiovascular events, and total CVD, defined as a composite outcome that included incident heart attack, stroke, coronary revascularization, cardiovascular mortality, carotid artery surgery, peripheral artery surgery, and unstable angina requiring

#### hospitalization.

#### The results

During follow-up, there were 1,053 cases of cancer. Total cancer incidence did not differ between the MVM and placebo groups. There was also no effect of MVM on cancer incidence in participants with a history of cancer. In terms of secondary outcomes, there was no difference between MVM and placebo for the incidence of breast cancer, colorectal cancer, prostate cancer, or melanoma. However, MVM decreased the incidence of lung cancer by 38%, compared to placebo.

During follow-up, there were 866 cases of CVD. Total CVD incidence did not differ between the MVM and placebo groups. There was also no difference between groups for individual cardiovascular events, CVD mortality, or all-cause mortality.

#### Note

This trial was limited by a short intervention. A longer intervention duration might be needed to observe a decrease in cancer and CVD incidence with MVM supplementation. Another limitation is the population that was studied. Among the participants, only 35% reported consuming less than 4 servings of fruit and vegetables per day, and only 4% were current smokers, although 41.3% were former smokers. Therefore, the results may not be generalizable to less health-conscious populations.

The researchers did not adjust for multiple comparisons, despite the inclusion of several outcomes, which increases the risk of false-positive results. Therefore, the secondary outcomes should be considered exploratory.

#### The big picture

The rationale behind advocating for the use of MVM supplements to prevent CVD and cancer is primarily related to the role of inflammation and oxidative stress in the development of these diseases and that several nutrients are known to have antioxidant and anti-inflammatory effects.<sup>[101]</sup> Additionally, the inadequacy of certain nutrients (e.g., vitamin A, vitamin D) impairs normal immune function, which may increase the risk of cancer, and the inadequacy of other nutrients (e.g., potassium) is associated with elevations in blood pressure and an increased risk of cardiovascular disease.<sup>[102]</sup>

Despite the mechanistic plausibility of MVM supplements being able to reduce the risk of CVD and cancer and the popularity of these supplements, there is a dearth of evidence from long-term randomized controlled trials to support their use. Besides the present study, there has been one other large-scale randomized controlled trial that assessed the effects of a broad-spectrum MVM supplement on cancer and CVD incidence. It included 14,641 male physicians (average age of 64) and found that, compared to a placebo, a MVM supplement reduced the incidence of total cancer by 8% over a median follow-up of 11.2 years.<sup>[103]</sup> However, there was no effect on total CVD incidence.<sup>[104]</sup> People who volunteer to participate in these types of studies are typically interested in healthy behaviors. Notably, 4% of the male physicians were current smokers, and 76% used aspirin, which supports the assumption that they were more health-conscious than the general population. This limitation was also present in the summarized study.

Virtually all nutrients have a nonlinear, inverted U-shaped association with optimum physiological function.<sup>[105]</sup> Very low nutrient levels in the diet or tissues result in poor function, and as nutrient levels increase, so does function. Optimum function can occur over a fairly wide range of nutrient levels due to individual differences, but at some point, higher nutrient levels become toxic and counterproductive.

In these studies, most of the participants were likely consuming a healthy and balanced diet, so there generally weren't any nutrient inadequacies or deficiencies present for the MVM to fix,<sup>[105]</sup> which is the general use for these products.

Another large-scale randomized controlled trial published in 2004 assigned participants to receive either a supplement containing vitamin C, vitamin E, beta-carotene, selenium, and zinc or a placebo over a median follow-up of 7.5 years.<sup>[106]</sup> The researchers found a 31% reduced incidence of total cancer in men who received the nutrient supplement compared to men who received the placebo, but there was no effect in women. There was also no effect of the nutrient supplement on CVD incidence.

The data from observational studies are mixed, but the majority of studies have found no association between MVM supplement use and CVD and cancer risk.<sup>[107][102][108]</sup>

Altogether, there is weak evidence to support the efficacy of MVM supplements for decreasing CVD and cancer risk in generally healthy people. But that doesn't necessarily mean that MVM supplements serve no purpose, it's just that their utility is reserved for certain populations. For example, MVM supplements may provide health benefits for older adults, pregnant women, people consuming a low-calorie diet for weight loss or due to poor appetite from an illness, and people consuming a strict vegan diet or a diet that excludes one or more food groups.<sup>[109]</sup>

Many healthy people who consume a balanced diet view MVM supplements as an "insurance policy" to help achieve adequate micronutrient intake. This is a fine approach, as micronutrient gaps can occur from time to time despite a balanced diet, and the long-term safety of MVM supplements doesn't seem to be a concern.<sup>[110]</sup> However, the available evidence does not demonstrate that MVM supplements reliably provide a health benefit for healthy people with adequate micronutrient intake, so the benefit-cost ratio of this approach should be considered on an individual basis. Further long-term randomized controlled trials are needed to confirm whether MVM supplements provide a health benefit to healthy people consuming a balanced diet.

#### #EditorsPick, #Dietitians

#### Can artificial sweeteners increase cancer risk?

High intakes of artificial sweeteners were associated with a 15% increased cancer risk over a median of 7.7 years. However, there were a number of caveats that precluded establishing a causal link.

#### Background

Artificial sweeteners have long been a source of controversy, despite their approval for use in foods and beverages by authoritative bodies such as the U.S. Food and Drug Administration and the European Food Safety Authority. Among the most cited concerns is their potential to increase cancer risk. While some evidence links these sweeteners to cancer in rodents, data on humans are scarce.

#### The study

This cohort study assessed the association between artificial sweetener intake and cancer risk. The authors assessed dietary intake and consumption of artificial sweeteners from 102,865 people in France twice per year between 2009 and 2021 via three nonconsecutive web-based 24-hour dietary records randomly assigned over 15 days (two weekdays and one weekend day). Baseline dietary intakes were evaluated by averaging all 24-hour dietary records during the first two years of follow-up.

The authors determined the associations based on total artificial sweetener intake (acesulfame-K, aspartame, cyclamates, saccharin, sucralose, thaumatin, neohesperidin dihydrochalcone, steviol glycosides, and salt of aspartame-acesulfame) and assessed acesulfame-K, aspartame, and sucralose individually. They included total cancer risk and risk for breast, prostate, and obesity-related cancers (colorectal, stomach, liver, mouth, pharynx, larynx, oesophageal, breast, ovarian, endometrial, and prostate cancers) as outcomes.

The authors adjusted for the following potential confounders:

- Age
- Sex (except for breast and prostate cancer analysis)
- Education level
- Physical activity
- Smoking
- BMI
- Height
- Weight gain during follow-up
- Presence of diabetes
- Family history of cancer

- Number of 24-hour dietary records completed
- Baseline intake of calories, alcohol, sodium, saturated fat, fiber, total sugar, fruits and vegetables, whole-grain foods, and dairy products

In their analysis, the authors categorized participants as "high" consumers of artificial sweeteners (those consuming above the median intake among consumers), "low" consumers (those consuming less than the median intake) and nonconsumers. The authors also categorized participants based on artificial sweeteners intake and total sugar intake (less than or at least 100 g/day) to compare the risk associated with sugar intake to that of artificial sweeteners.

#### The results

Compared to nonconsumers, higher consumers tended to be younger, women, smokers, less physically active, more educated, and more likely to have prevalent diabetes. They had lower intakes of energy, alcohol, saturated fats, fiber, fruit and vegetables, and whole-grain food and higher intakes of sodium, total sugar, dairy products, sugary foods and drinks, and unsweetened nonalcoholic beverages. The main artificial sweetener used by participants was aspartame (58% of artificial sweetener intake), followed by accesulfame-K (29%) and sucralose (10%). All participants' intakes of aspartame and acesulfame-K were below the *acceptable daily intakes* (ADIs) of 40 mg/kg body weight/day and 9 mg/kg body weight/day, respectively. Only 5 participants exceeded the ADI of 15 mg/kg body weight/day for sucralose. Soft drinks, table-top sweeteners, and yogurt/cottage cheese were the main contributors to total artificial sweetener intake, accounting for 53%, 29%, and 8% of intakes, respectively.

Compared to nonconsumers, high consumers had a 13% higher risk of overall cancer over a median follow-up of 7.7 years. When the authors stratified by type of sweetener, they found that aspartame and acesulfame-K were associated with a 15% and 13% higher risk for total cancer, respectively. When the authors stratified by cancer site, high consumers had a 13% higher risk for obesity-related cancers. In addition, high consumers of aspartame had a 22% higher risk for breast cancer and a 15% higher risk for obesity cancers.

Exposure	Measure	Non- consumers	Low consumers	High consumers
Total artificial sweeteners	Incident cases/ participants (overall % risk)	2,013/ 64,892 (3.10% risk)	744/18,986 (3.92% risk)	601/18,987 (3.17% risk)

### Total cancer outcomes

Exposure	Measure	Non- consumers	Low consumers	High consumers
Total artificial sweeteners	Hazard ratio (95% CI) (adjusted for age and sex only)	1	1.26 (1.16 to 1.37)	1.19 (1.08 to 1.30)
Total artificial sweeteners	Hazard ratio (95% CI) (fully adjusted)	1	1.14 (1.05 to 1.25)	1.13 (1.03 to 1.25)
Aspartame	Incident cases/ participants (overall % risk)	2,309/ 74,169 (3.11% risk)	572/14,345 (3.99% risk)	477/14,351 (3.32% risk)
Aspartame	Hazard ratio(95% CI) (adjusted for age and sex only)	1	1.21 (1.11 to 1.33)	1.18 (1.07 to 1.31)
Aspartame	Hazard ratio (fully adjusted)	1	1.12 (1.02 to 1.23)	1.15 (1.03 to 1.28)
Acesulfame- K	Incident cases/ participants (overall risk)	2,096/ 67,662 (3.10% risk)	766/17,601 (4.35% risk)	496/17,602 (2.82% risk)
Acesulfame- K	Hazard ratio(adjusted for age and sex only)	1	1.22 (1.12 to 1.33)	1.19 (1.07 to 1.33)
Acesulfame- K	Hazard ratio (fully adjusted)	1	1.12 (1.03 to 1.22)	1.13 (1.01 to 1.26)
Sucralose	Incident cases/ participants (overall risk)	2,883/ 88,867 (3.24%	288/7,005 (4.11% risk)	187/6,993 (2.67% risk)

Exposure	Measure	Non- consumers	Low consumers	High consumers
		risk)		
Sucralose	Hazard ratio (adjusted for age and sex only)	1	1.20 (1.06 to 1.35)	1.00 (0.86 to 1.17)
Sucralose	Hazard ratio (fully adjusted)	1	1.03 (0.91 to 1.17)(nonsignificant)	0.96 (0.82 to 1.12) (nonsignificant)

The authors also found that high sugar intake was associated with increased cancer risk. However, there was no difference in risk between high consumers of artificial sweeteners consuming less than 100 grams of sugar per day and nonconsumers of artificial sweeteners consuming at least 100 grams of sugar per day. The highest risk for cancer was observed in participants with a high intake of artificial sweeteners and intake of at least 100 grams of sugar per day.

#### Note

At first glance, this study suggests that artificial sweeteners can increase cancer risk, but several caveats have to be considered:

- As this was an observational study, it cannot be used to establish whether artificial sweeteners cause cancer. Though the authors did adjust for potential confounders, there may have been other confounding variables that weren't adjusted for. For example, high artificial sweetener consumers might also have a high intake of fast food (people might order artificially sweetened beverages with their meals) or processed foods, which often contain artificial sweeteners. However, this study does justify future research into causality. As the authors note, the causal claim could be bolstered or negated by Mendelian randomization studies down the road.
- Another 2019 analysis from the same cohort found that artificially sweetened beverages were not associated with cancer, whereas sugary drink consumption was associated with cancer.<sup>[149]</sup>
- While the results are statistically significant, it's worth considering whether the results are *clinically* significant. That's why it's important to look at overall cancer risk for each group of participants, as opposed to relative risk. Of the 64,892 people classified as "nonconsumers," there were 2,013 incident cases of cancer (a 3.10% risk). Of the 18,986 people classified as "low consumers," there were 744 incident cases of cancer (a 3.92% risk). Of the 18,987 participants classified as "high consumers," there were 601 incident cases of cancer (a 3.17% risk).

• Low consumers had a slightly higher risk for cancer than high consumers, though this difference was not tested for statistical significance. If artificial sweeteners do increase cancer risk, one would expect high consumers to be at the highest risk.

#### The big picture

The March 2022 issue of Study Summaries includes a review that concluded artificial sweeteners were not genotoxic, meaning they don't cause DNA or chromosomal damage, and as such are likely not carcinogenic. However, as noted in that review, that study and several other narrative and systematic reviews assessing the genotoxicity potential of artificial sweeteners were partially funded by the American Beverage Association.

#EditorsPick, #Dietitians, #SportsNutrition

▲ Back to Table of Contents

## Cognition & Memory

#### Iron and cognition in adolescents 🗵

This systematic review found a complex and somewhat unclear relationship between iron status and anemia and the impact of iron-containing interventions on cognition and academic performance in adolescents.

#### Background

*Iron-deficiency anemia* (IDA) is estimated to be the leading cause of *disability-adjusted life years* (DALYs) lost in adolescents. Iron-containing interventions are commonly integrated into school-based programs that are valued for their perceived improvements in academic performance, but does the evidence indicate that they work?

#### The study

This systematic review of 50 studies (26 cross-sectional studies and 24 experimental trials) in adolescents evaluated the association between iron status or anemia and measures of cognition or academic performance. It also assessed whether iron-containing interventions improve measures of cognition or academic performance. All of the included studies had an average participant age of 10–19, and 34% of the studies included female participants.

The cross-sectional studies included sample sizes ranging from 30 to 5,398 participants and used various different methods to evaluate nutrition and anemia status (e.g., hemoglobin levels, iron intake). The experimental trials included food-based and iron-only or iron+micronutrient supplementation interventions that lasted 1–14 months. Various types of iron were included at different doses, and sample sizes ranged from 51 to 808 participants.

Learning and cognition outcomes included IQ testing, grades, and specific cognition tests, among others. The included experimental trials were also assessed for risk of bias.

#### The results

The authors reported the following findings from their analysis:

- Iron status and/or anemia were associated with academic performance in most of the studies. Nearly all iron-containing interventions reported positive findings as well.
- Iron status and/or anemia were not associated with attention and concentration in most studies, although iron-containing interventions reported positive findings more often than not.
- Most of the cross-sectional and experimental studies reported no associations with or changes in

intelligence and memory/recall.

• Nearly all supplementation trials had a moderate or high risk of bias.

#### Note

These results should be interpreted with caution because the outcomes were evaluated with an extremely broad range of assessment methods and interventions and most trials presented a moderate or high risk of bias.

#### #Dietitians

#### Can eating more fiber reduce the risk for dementia? 🗷

*In this cohort study, dietary fiber intake — especially soluble fiber intake — was associated with reduced risk for dementia.* 

#### Background

Preliminary animal research suggests that dietary fiber, especially *soluble* fiber, could have a neuroprotective effect.<sup>[181]</sup> However, this effect needed to be explored in humans.

#### The study

This cohort study assessed whether total dietary fiber intake and fiber type (soluble vs. insoluble) were associated with a reduced risk for dementia (primary outcome) among 3,739 adults in Japan (ages 40–64). As secondary outcomes, the authors assessed whether a history of stroke or the type of fiber-containing foods consumed (potatoes, vegetables, and fruits) modified the association between fiber intake and disabling dementia.

The participants completed 24-hour dietary recalls between 1985 and 1999 to assess dietary fiber intake and the types of fiber-containing foods consumed. The authors assessed incident disabling dementia (dementia that required care) from 1999 to 2020 and further stratified the participants with disabling dementia based on whether or not they had a history of stroke.

In their analysis, the authors adjusted for age, smoking status, alcohol consumption, total calorie intake, and fish, meat, and sodium consumption.

#### The results

Over a median of 19.7 years of follow-up, 670 cases of disabling dementia occurred.

Total fiber intake was linearly associated with a reduced risk for disabling dementia. Participants in the highest quartile of dietary fiber intake had a 26% lower risk of disabling dementia than those in the lowest quartile.

When the authors stratified the participants based on a history of stroke, the inverse association was only

significant among participants without a history of stroke. When they were stratified by type of dietary fiber, only soluble fiber intake was significantly associated with a reduced risk of dementia, although the inverse association between insoluble fiber intake and stroke trended towards significance.

When the authors assessed types of fiber-containing foods, potato intake was inversely associated with disabling dementia, whereas there was no association between fruit or vegetable intake and disabling dementia.

#### #Dietitians, #AlzheimersDisease

#### Neurocognitive effects of cocoa and red berry powders 🗷

This 12-week trial found that an increased intake of flavanols and/or anthocyanins did not improve summed measures of cognitive function, and only results for certain executive function tests improved.

#### Background

Polyphenols appear to improve cognitive function and prevent cognitive decline.<sup>[92]</sup> Can flavonols and anthocyanins from cocoa and red berries, respectively, affect biomarkers of brain health and improve cognitive performance in older adults?

#### The study

This 12-week randomized controlled trial involved 59 healthy participants (average age of 58; 29% male) who consumed either a cocoa powder (200 milligrams of flavanols daily), a red-berry-mixture powder (100 milligrams of anthocyanins daily), or both.

The results of various neurocognitive tests, including the Spain-Complutense Verbal Learning Test, the Stroop Task, and the Tower of London Test, were summed according to three main measures of cognitive function: memory, processing speed and attention, and working memory.

The researchers also analyzed serum biomarker levels of brain health such as *brain derived neurotrophic factor* (BDNF) and *nerve growth factor receptor* (NGF-R) and inflammation such as *interleukin-6* (IL-6). Total polyphenols in urine (normalized for urine creatinine levels) and anthropometric (body) measurements were also collected.

#### The results

No changes were observed in any of the summed measures of cognitive function or serum levels of BDNF and NGF-R following the increased intake of flavonols and/or anthocyanins. A few results for certain executive function tests, such as the time to start and finish the Tower of London Test, did improve following the intervention.

Creatinine-corrected urine polyphenol content increased in the cocoa powder and combination groups (accompanied by decreases in serum IL-6 levels), while the red berries group tended toward, but did not

reach, a significant increase (p=0.059).

A difference in body fat and water percentage was noted for between-group comparisons, with the cocoa powder group displaying greater body fat and lower water content, but no changes were noted following the intervention.

#### Note

The intricacies of these results should be interpreted with caution because systemic (as opposed to localized) blood samples were analyzed for some brain health biomarkers, the authors did not analyze the polyphenol powders to confirm that the manufacturer labels were accurate, and there were some differences in baseline measures between groups.

#### #Dietitians

#### Iron supplementation and neurocognitive development

This cross-sectional study reported poorer neurocognitive function during adolescence for participants who were nonanemic and iron supplemented at a relatively high level during ages 6–12 months, as well as those that were slightly anemic and not iron supplemented.

#### Background

Micronutrient intake tends to have a "sweet spot". Iron deficiency is the world's leading nutrient deficiency and is of particular concern during infancy because iron is an essential nutrient for normal brain development. However, overexposure to iron within 6–24 months of age may also cause harm to the immune system and microflora and compete with other trace elements for absorption. Does iron supplementation during the early months of life negatively influence neurocognition?

#### The study

This cross-sectional study involved 562 Chilean adolescents (average age of 16; 47% male) who participated in a randomized controlled iron supplementation trial during their infancy (ages 6–12 months). Overall, 346 participants consumed an iron-fortified formula (12.7 mg/L) or liquid vitamins with 15 milligrams of elemental iron (ferrous sulfate), and 216 consumed cow's milk without iron or liquid vitamins without iron.

The participants completed a battery of tests to assess neurocognitive development, including the Beery-Buktenica Test of Visual-Motor Integration, the Wide Range Achievement Test-revised (arithmetic-based), the Wechsler Intelligence Scale for Children-Revised, the Trail Making Test, and the Wisconsin Card Sorting Test.

The analysis was adjusted for participant and maternal demographics, infant growth, and family socioeconomic status.

#### The results

Iron-supplemented participants had poorer visual-motor integration, poorer quantitative reasoning skills, and more errors on neurocognitive tasks. Greater intake of iron-fortified formulas was associated with lower arithmetic achievement.

Poorer neurocognitive development was associated with iron supplementation in adolescents who demonstrated high hemoglobin levels at 6 months, as well as adolescents who demonstrated low 6-month hemoglobin levels and did not receive supplemental iron.

#### Note

Infant iron status can be influenced by maternal iron status and nonnutritional factors, as well as nutritional intake, and many of these factors were not monitored in this study.

#### #Dietitians

#### Can omega-3 fatty acids boost cognitive performance in healthy adults?

Supplementation with omega-3 fatty acids did not improve cognitive performance in healthy adults, regardless of age and apolipoprotein E genotype, but had a small benefit for adults with low episodic memory at baseline.

#### Background

Omega-3 fatty acids are associated with lower cognitive decline and a lower risk of Alzheimer's disease in older adults.<sup>[205][206]</sup> However, the question of whether omega-3 fatty acids can improve cognitive performance in healthy adults remains unanswered, with clinical trials showing conflicting results.<sup>[207][208][209][210]</sup>

One possible explanation is that age and genetic predispositions might influence the beneficial effects of omega-3 fatty acids. For instance, carriers of the apolipoprotein E genotype (a genetic risk factor for certain neurological disorders such as dementia)<sup>[211]</sup> experience fewer benefits from omega-3 fatty acids for prevention of cognitive decline.<sup>[208]</sup> This study examined whether omega-3 fatty acids can improve cognitive performance in healthy adults when controlling for age and apolipoprotein E genotype.

#### The study

This 6-month randomized-controlled trial of 193 healthy adults (aged 20–80) examined whether supplementation with omega-3 fatty acids (2.5 grams per day) improves cognitive performance compared to a placebo.

The primary outcomes were visuospatial ability and working memory. The secondary outcomes were episodic memory and executive function. The researchers also investigated whether the outcomes were influenced by age or apolipoprotein E genotype.

#### The results

Supplementation with omega-3 fatty acids did not improve cognitive performance in any of the measured outcomes. Additionally, age and apolipoprotein E genotype did not influence the outcomes.

However, for participants who had low episodic memory scores, omega-3 fatty acids had some benefits because their scores were improved to normal levels.

#### Note

Similar to previous trials,<sup>[208][212]</sup> the results of this study suggest that omega-3 fatty acids do not improve cognitive performance in cognitively healthy adults but may be useful for those with low cognitive scores. However, these results should be viewed with caution because the researchers did not intend to analyze this outcome at the beginning of the study, and the differences were borderline significant.

#Dietitians, #AlzheimersDisease

▲ Back to Table of Contents

## 🗞 Diabetes & Blood Sugar

#### Sweet news about low- and zero-calorie beverages 🗷

This network meta-analysis found that, to reduce body weight and cardiometabolic risk, replacing sugarsweetened beverages with low- or zero-calorie beverages worked better than replacing them with water.

#### Background

High consumption of *sugar-sweetened beverages* (SSBs) is strongly associated with an increased risk of obesity and cardiometabolic complications. Although many people use *low-calorie (and zero-calorie) sweetened beverages* (LCSBs) to replace SSBs, their use remains controversial.

#### The study

This network meta-analysis of assessed the effects of the following interventions on body weight and cardiometabolic risk factors:

- Substituting SSBs with LCSBs
- Substituting SSBs with water
- Substituting water with LCSBs

The inclusion criteria specified that the *randomized controlled trials* (RCTs) must be at least 2 weeks long and excluded studies that assessed sweeteners in nonbeverage form (e.g., tablets) or in fortified or nutrient-dense beverages (e.g., milk and juice). The included studies assessed participants both with and without diabetes.

The primary outcome was body weight. The authors also assessed the following secondary outcomes:

- BMI
- Body fat percentage
- Waist circumference
- HbA1C
- Fasting blood glucose
- 2-hour postprandial glucose during a 75-gram oral glucose tolerance test
- Fasting plasma insulin
- HOMA-IR

- LDL-C
- HDL-C
- Triglycerides
- Total cholesterol
- Non-HDL cholesterol
- Systolic blood pressure
- Diastolic blood pressure
- Liver fat
- Liver enzymes alanine aminotransferase and aspartate aminotransferase (ALT and AST)
- Uric acid

The authors assessed 17 RCTs with 24 trial comparisons, including 1,733 adults (75% women; average age of 33; median BMI of 31). The median follow-up period was 12 weeks, with studies ranging from 3 to 52 weeks in duration. Nine RCTs exclusively assessed participants with overweight or obesity, and 1 trial exclusively assessed patients with type 2 diabetes.

Eight RCTs (11 comparisons) reported the low-calorie or zero-calorie sweetener used: 7 comparisons used aspartame, and 1 comparison each assessed an aspartame and acesulfame potassium blend, saccharin, rebaudioside A, and sucralose.

LCSBs substituted for SSBs in 12 RCTs, water substituted for SSBs in 3 RCTs, and LCSBs substituted for water in 9 RCTs.

Eight RCTs were funded by agencies (government, not-for-profit agency, or university), 4 were funded by industry, and 5 were funded by a combination of agency and industry.

#### The results

Substituting SSBs with LCSBs reduced body weight (-1.06 kg), BMI (-0.32), body fat percentage (-0.6%), and liver fat. Substituting SSBs with water was not associated with any significant outcome (although the results tended to favor water for nearly all outcomes). Substituting water with LCSBs reduced body weight (-1.07 kg), increased HbA1C (+0.21%), and reduced systolic blood pressure (-2.63 mm Hg).

The certainty of evidence for body weight was moderate for substituting SSBs with LCSBs, low for substituting SSBs with water, and low for substituting water with LCSBs.

#### Note

The authors declared several conflicts of interest — they reported receiving support from companies such

as Loblaws Companies Limited (a Canadian food distributor), the National Honey Board, the Canadian Sugar Institute, Ocean Spray, General Mills, the International Sweeteners Association, Danone, Unilever, Kelloggs, Pepsi-Co, Sun-Maid, and Nestlé.

#### #Dietitians, #ConflictOfInterest

#### Supplementing antidiabetic drugs with micronutrients for glycemic control 🗷

This meta-analysis found that supplementing antidiabetic drugs with chromium, vitamin C, vitamin E, or coenzyme Q10 improved glycemic control in people with type 2 diabetes.

#### Background

Glycemic control is critical for preventing complications in people with *type 2 diabetes* (T2D).<sup>[62][63]</sup> Metaanalyses of randomized controlled trials suggest that supplementing with certain nutrients can improve some parameters of glycemic control in people with T2D.<sup>[64][65][66]</sup> However, the effect of add-on nutrient supplements (i.e., used alongside antidiabetic drugs) on glycemic control had yet to be investigated.

#### The study

This meta-analysis of 119 randomized controlled trials examined the effect of adding nutrient supplements to antidiabetic therapies (e.g., metformin, insulin) on glycemic control in people with T2D.

Nine nutrient supplements were analyzed:

- Vitamin D (29 studies; 400–6,000 IU/day)
- Omega-3 fatty acids (26 studies; 1–12 grams/day)
- Vitamin E (21 studies; 200–1,600 IU/day),
- Chromium (16 studies; 200–1,000 micrograms/day)
- Vitamin C (12 studies; 200–1,000 milligrams/day)
- Coenzyme Q10 (CoQ10; 11 studies; 150–200 milligrams/day)
- Zinc (5 studies; 30–240 milligrams/day)
- Alpha-lipoic acid (3 studies; 300–800 milligrams/day)
- Selenium (2 studies; 200 micrograms/day).

The outcomes assessed were HbA1c, fasting blood glucose, and HOMA-IR.

#### The results

Chromium improved HbA1c (−0.39%), fasting blood glucose (−16.30 mg/dL), and HOMA-IR (−2.48). The effect of chromium was greater in participants with an HbA1c ≥ 8%, and chromium picolinate was the

most effective formulation.

Additionally, vitamin C improved HbA1c (-0.37%) and fasting blood glucose (-11.96 mg/dL); CoQ10 improved HbA1c (-0.23%) and fasting blood glucose (-8.84 mg/dL); vitamin E improved HbA1c (-0.23%) and HOMA-IR (-0.37); and omega-3 fatty acids improved HbA1c (-0.26%).

#### Note

There was moderate heterogeneity in the majority of the analyses, and the researchers were unable to identify the causes of heterogeneity in some of these, which reduces confidence in the findings.

#### **#Dietitians**

#### Astaxanthin's effect on oxidative stress and inflammation 🗷

This meta-analysis of 12 randomized controlled trials reports that astaxanthin can reduce some biomarkers of lipid peroxidation (involved in cell damage) and inflammation and may improve endogenous antioxidant enzymatic activity (which helps protect against cell damage), mostly in type 2 diabetes patients.

#### Background

Supplementation with astaxanthin has been shown to reduce biomarkers of oxidative stress and inflammation in animal and in vitro studies, but does this hold true for human trials?

#### The study

This meta-analysis of 12 *randomized controlled trials* (RCTs) followed a total of 380 participants, who took an astaxanthin supplement (4–20 milligrams/day) or a placebo, for 1–12 months. The participants were monitored for changes in biomarkers of oxidative stress and inflammation.

#### The results

Astaxanthin reduced blood concentrations of malondialdehyde (a biomarker of lipid peroxidation, which is involved in cell damage) and interleukin-6 (a biomarker of inflammation), despite a high or medium level of heterogeneity (i.e., variability in data) among the 6 included studies for each analysis. These reductions were most notable in participants with type 2 diabetes. There were no changes in blood C-reactive protein (6 studies), tumor necrosis factor-alpha (4 studies), or total antioxidant capacity (3 studies).

The authors reported that astaxanthin can improve antioxidant enzymatic activity (superoxide dismutase, which helps protect against cell damage) and isoprostane levels (another indicator of lipid peroxidation), although this was primarily based on a single study.<sup>[114]</sup>

#### Note

These improvements may be attributed to the high heterogeneity, sensitivity, and specificity of

biomarkers and assays.

Only a few biomarkers were measured in enough studies for a meaningful analysis, and many biomarkers can be very sensitive or depend on the assay or sample used. <sup>[14][15]</sup>

Malondialdehyde analysis has several limitations, including low stability and recovery and poor reproducibility and specificity.<sup>[115]</sup>

#Dietitians

▲ Back to Table of Contents

## **Diets & Foods**

#### Are carbs to blame for the obesity epidemic?

When it comes to weight management, energy balance is king, not low-carbohydrate diets.

#### Background

The authors of a 2021 narrative review<sup>[68]</sup> argued against the energy balance model of obesity. They instead argued for the *carbohydrate-insulin model* (CIM), which asserts that a high-glycemic diet increases fat gain and that this fat gain drives a positive energy balance, perpetuating a cycle of continued excess weight gain. Additionally, the authors of the narrative review stated that the EBM doesn't consider "biological mechanisms that promote weight gain."

The role of carbohydrates and insulin in the etiology of obesity continues to be debated. What does the evidence say?

#### The study

The authors of the current narrative review responded to the aforementioned 2021 review, defending the EBM model. They described the EBM, CIM, and relevant data from studies assessing rodents, human genetics, epidemiology, and dietary and pharmacological interventions.

#### The results

**The Energy Balance Model of Obesity:** The EBM states that the brain is the main organ responsible for body weight regulation, coordinating with the endocrine, metabolic, and nervous systems. The brain modulates food intake unconsciously, responding to environmental influences and the body's energy needs. This occurs through short-term signals sent to the brain between and during meals (e.g., ghrelin, PYY, GLP-1) and long-term signals (e.g., leptin) released from adipose tissue, which tell the brain how much stored energy (i.e., body fat) is available. Thus, while *daily* energy intake and energy balance can be highly variable, regulation of energy balance is achieved over *long* durations.

#### **The Brain:** Master regulator of energy balance



In addition, macronutrient intake affects whole-body net oxidation rates of carbohydrate, fat, and protein, so that overall energy imbalances are primarily reflected as fat imbalances, regardless of the macronutrient composition of the diet. For example, if someone eats in an energy surplus, with the excess calories primarily derived from protein, the body will convert the excess protein to glucose, and fat oxidation (or "fat-burning") will decrease because protein is being used as fuel, resulting in a positive fat balance.

The authors state that the characterization of the EMB in the aforementioned narrative review as a theoretical model that "essentially disregards knowledge about the biological influences on fat storage"<sup>[68]</sup> is incorrect and is an oversimplification of the EBM.

The Carbohydrate-Insulin Model of Obesity: The CIM states that obesity results from high carbohydrate intake driving excess insulin secretion, causing adipose tissue to accumulate and "trap" fat, preventing nonadipose tissues from getting fuel. The authors of the current review noted that fat storage can occur in the absence of dietary carbohydrates or increases in insulin and that many factors beyond dietary carbohydrates determine insulin secretion.

# • **Digging Deeper:** Do you need insulin to store body fat?

As described by the authors of the current review, a core tenant of the CIM is that carbohydrates stimulate insulin secretion and that insulin promotes body fat storage. However, the provision of triglycerides intravenously promotes body fat storage, even when insulin is at fasting levels.<sup>[69][70]</sup> In addition, high insulin levels in a fasted state do not promote fat storage.<sup>[71][72]</sup> Thus, while insulin does promote body fat storage, largely by suppressing the breakdown of fat cells in adipose tissue,<sup>[73]</sup> net fat storage is determined by the energy available to store (i.e., calories in) and the energy that is oxidized (i.e., calories out).

The authors also noted that the CIM, as described in the recent narrative review, is different from its previous iterations in that "all obesogenic factors (e.g., amount of dietary protein, micronutrients, poor sleep, stress, physical inactivity, and environmental endocrine-disrupting chemicals) affect insulin secretion or adipocyte biology directly, with increased energy intake and decreased energy expenditure as necessary downstream consequences." In this way, the authors state that the current CIM is an "oversimplified version of the EBM, with a focus on glycemic load as the main driver of excess energy intake."

#### Evaluation of the EBM and CIM:

- Rodent studies: The authors noted that most standard laboratory rodent diets are high in carbohydrates and do not induce obesity, whereas diets with lower percent carbohydrates and higher percent fat often induce obesity. Additionally, standard laboratory rodent diets contain carbohydrates derived from corn starch, maltodextrin, and sucrose, all of which have a high glycemic index.
- Human genetics: The EBM implicates the brain as the primary organ responsible for obesity, whereas the CIM implicates adipose tissue. Other than rare mutations in the leptin gene, no genetic disorders primarily affecting fat calls or insulin have been reported to cause obesity. In contrast, genome-wide association and gene expression studies have determined that variations in adiposity between people are primarily due to differences in genes most highly expressed in the brain.
- Human epidemiological studies: Evidence does not suggest that carbohydrate intake is the main driver of the U.S. obesity epidemic. Epidemiological evidence finds that obesity risk is based on

long-term adherence to various healthful dietary patterns, with variable carbohydrate contents.

- Human diet intervention studies: The CIM predicts that long-term weight loss occurs by reducing dietary carbohydrate and glycemic load, resulting in less hunger, lower food intake, and increased energy levels.<sup>[68]</sup> However, diet intervention studies have found that low glycemic load diets do not result in greater weight loss than higher glycemic load diets. Additionally, long-term diet intervention studies comparing low-fat and low-carbohydrate diets controlling for protein intake do not report a difference in weight loss.
- Human pharmacological intervention studies: The CIM states that high insulin levels induce weight gain by inhibiting adipose tissue lipolysis, thereby trapping fat in fat cells.<sup>[68]</sup> However, inhibiting adipose lipolysis with acipimox treatment does not affect energy intake, resting energy expenditure, or body composition, and GLP-1 receptor agonists (medications used to treat obesity) acutely increase insulin secretion.

#### The big picture

The controversy surrounding carbohydrates, insulin, and obesity is unlikely to end anytime soon. As such, it's worth revisiting prior issues of Study Summaries that have shed light on the topic:

The September 2020 issue of Study Summaries includes a review of a secondary analysis of another randomized controlled trial that analyzed the estimated caloric requirements of participants on either a low- or high-carb diet during a weight-maintenance period. The average estimated caloric requirements were about 245 kcal/day higher in the low-carb group than in the high-carb group. However, the interindividual variability was high, and some of the methodology used in the original trial has been hotly contested.

The December 2020 issue of Study Summaries includes a review of a 4-week crossover study comparing the effects of a plant-based *low-carbohydrate diet* (LCD: 10% carbs, 50% fat, 40% protein), an animal-based LCD (10% carbs, 60% fat, and 30% protein), and a *low-fat diet* (LFD: 61% carbs, 21% fat, and 18% protein) on body composition and blood markers. All three diets resulted in weight loss, but the plant-based LCD group lost more weight than the LFD.

The January 2021 issue of Study Summaries includes a review of a meta-analysis of 38 randomized controlled trials that investigated the effects of low-carb diets, low-fat diets, or both, on weight loss and blood lipids. Low-carb dieters lost about one additional kilogram of weight overall, and this difference was most notable when the diets ranged from 6 to 12 months. Triglycerides were reduced more by low-carb diets, whereas LDL-C, HDL-C, and total cholesterol were reduced more by low-fat diets.

The same January issue of Study Summaries includes a review of a systematic review of 8 randomized controlled trials comparing saturating fat intakes and measurements of body weight, blood glucose, cholesterol, and blood pressure among adults with a BMI of at least 25 who ate either a low-carb, high-fat

diet (LCHF) or a low-fat diet (LF). Both diets resulted in significant weight reduction, improved blood glucose levels and inflammatory markers, and lowered blood pressure. The reduction in LDL cholesterol was stronger in the LF diet group, while increased HDL cholesterol and reduced triglycerides were observed in the VLCHF group.

The same January issue of Study Summaries includes a review of an 18-month study assessing the effects of a *low-carbohydrate Mediterranean diet* (LCMD) on hepatic fat content and visceral adipose tissue compared to a *low-fat diet* (LFD). The participants in the LCMD group had a greater reduction in hepatic fat content than the participants in the LFD group. After adjusting for changes in visceral adipose tissue, the LCMD group also experienced greater improvements in blood lipids, blood pressure, and cardiovascular risk score.

The March 2021 issue of Study Summaries includes a review of a crossover study in which participants followed a *low-carb diet* (LCD: 10% carbs, 75% fat) and a *low-fat diet* (LFD: 75% carbs, 10% fat) for two weeks each. The two diets led to similar weight loss (1–2 kg / 2.2–4.4 lb, over two weeks). However, the low-fat diet led to a greater reduction in fat mass, whereas the low-carb diet led to a greater reduction in fat mass.

The same March issue of Study Summaries includes a review of a meta-analysis of 18 randomized controlled trials that investigated the effects of a ketogenic diet compared to a low-fat control diet. The ketogenic diet reduced body weight, BMI, fat mass, fat-free mass, waist circumference and visceral fat, lean body mass, and body fat percentage, compared to a low-fat diet. Variability between studies was found for body weight, fat mass, and BMI. BMI was not reduced in studies that included only women.

The September 2021 issue of Study Summaries included a review of a meta-analysis of randomized controlled trials assessing the relative effectiveness of *low-fat/high-carb* (LFHC) and *low-carb/high-fat* (LCHF) diets on weight loss and cardiovascular risk factors. Compared to LFHC diets, LCHF diets resulted in a greater weight loss (-1.01 kg) and a greater increase in HDL-C (+7.7 mg/dL). However, LCHF diets resulted in a smaller decrease in total cholesterol and LDL-C (-24.4 and -22.8 mg/dL, respectively).

The December 2021 issue of Study Summaries includes a review of a 6-month, nonrandomized controlled trial in which participants consumed either a *low-carb diet* (LCD) or a *low-fat diet* (LFD). Compared to baseline, both diets improved triglycerides, HDL-C, diastolic blood pressure, fasting blood glucose, and waist circumference. The only significant difference between groups was for triglycerides, which showed greater reductions with the LFD.

The February 2022 issue of Study Summaries includes a review of a 6-month randomized controlled trial that randomized people with type 2 diabetes to follow a *low-carb, high-protein diet* (LCHP: 14% carbohydrates, 28% protein, 58% fat) or a *low-fat diet* (LFD: 53% carbohydrates, 17% protein, 30% fat). Body weight decreased in the LCHP group compared to the LF diet (-4.1 vs. -1.0 kg), and markers of glycemic control improved to a greater extent in the LCHP group compared to the LF diet.

The March 2022 issue of Study Summaries includes a review of a meta-analysis of 61 randomized controlled trials comparing the effects of *low-carb weight-reducing* (LCWR) diets with *balanced-carbohydrate weight-reducing* (BCWR) diets on body weight and cardiovascular risk factors among 6,925 participants with obesity. Participants without T2D experienced greater weight loss (-1.07 kg) in the low-carbohydrate diet group over 3 to 8.5 months, compared to the balanced-carbohydrate diet group over 1 to 2 years. Participants with T2D experienced greater weight loss (-1.26 kg) in the low-carbohydrate group over 3 to 6 months, compared to the balanced-carbohydrate group over 3 to 6 difference in weight loss between groups.

#### #EditorsPick, #Dietitians, #Obesity, #Type2Diabetes

#### Ultraprocessed food intake and mortality 2

This meta-analysis of prospective studies reported an increased risk of mortality associated with higher overall intakes of ultraprocessed food, sugar-sweetened beverages, artificially sweetened beverages, and processed/red meat.

#### Background

*Ultra processed food* (UPF) intake has been associated with overeating, noncommunicable disease, and mortality, but the NOVA system for classifying UPFs is often criticized for overly broad categorizations.

# The NOVA system for food categorization in a nutshell

The NOVA (not an acronym) classification categorizes foods into four groups differing in terms of the degree of processing:

- 1. Unprocessed or minimally processed foods: foods that can be eaten with little to no modification, although removing inedible parts, pasteurization, and drying is fine.
- 2. Processed culinary ingredients: food products derived from plants and animals but not meant to be consumed by themselves, like oil, butter, sugar, and salt. These are used to enhance or season unprocessed foods.
- 3. Processed foods: foods made by combining processed culinary ingredients with unprocessed foods. Examples include cheese, canned fish, fruits in syrup, etc.
- 4. Ultra-processed foods: edible combinations made mostly of substances derived from food

(flour, sugar, oil) and additives (minerals, preservatives) with little, if any, intact unprocessed food. Examples include soft drinks, snacks, and frozen meals.

How does the intake of subgroups of UPFs influence the risk of mortality?

#### The study

This meta-analysis included 40 prospective cohort studies, involving a total of 5,750,133 adult participants, that evaluated the association between UPF intake and risk of mortality.

The NOVA system was used to classify foods according to their extent of processing (e.g., none/minimal, culinary ingredients, combinations of the latter two categories, few whole/natural food components and additives).

The relative risk for all-cause mortality was compared between the highest vs. lowest intake of subgroups, including overall UPFs (5 studies), processed/red meat (22 studies), sugar-sweetened beverages (9 studies), artificially sweetened beverages (6 studies), and breakfast cereals (10 studies). Most of the included studies adjusted for age and sex, but not lifestyle or socioeconomic factors.

#### The results

Higher UPF, sugar-sweetened beverage, artificially sweetened beverage, and processed/red meat intakes were associated with an increased risk of mortality (by 29%, 11%, 14%, and 15%, respectively). A higher intake of breakfast cereals was associated with a 15% lower risk of mortality.

#### Note

Breakfast cereals are still considered to be UPFs but are often consumed in the mornings. A 2020 metaanalysis reported that eating breakfast is associated with a 25% lower risk of mortality.<sup>[129]</sup>

Check out this Study Deep Dive article, which gives more detail about UPFs and how they may influence eating habits and health.

#### #Dietitians

#### Associations between a vegetarian diet and bowel health 🗷

Vegetarians in this U.S. cohort consumed a relatively low amount of fiber and showed no differences in bowel health compared to nonvegetarians. However, some of the data are considered unreliable due to the small sample size in the vegetarian cohort.

#### Background

Western populations fail to consume the recommended amount of fiber of 25 to 30 grams per day. However, vegetarians eat an abundance of plant foods and presumably consume fiber at or above the recommended amount. High-fiber diets also promote bowel health and result in increased stool frequency. Is the vegetarian diet associated with less constipation and differences in defecating function than a nonvegetarian diet?

#### The study

This cross-sectional study of 9,531 omnivores and 212 self-identified vegetarians from the U.S. National Health and Nutrition Examination Survey (NHANES) explored the differences in bowel health among these two populations. Bowel health was measured using bowel movement frequency, the Bristol Stool Form Scale, and the Fecal Incontinence Severity Index.

#### The results

The vegetarians consumed fewer calories and lower moisture in food and beverages but had a higher fiber intake than the omnivores. Fiber intake among the vegetarian group was still relatively low (21 grams/day).

There were no differences in measures of bowel health between the vegetarian and omnivore groups.

#### Note

The researchers noted that they adhered to the National Center for Health Statistics Data Presentation Standards for Proportions,<sup>[286]</sup> and as such, the measures for constipation, bowel movement frequency (<3 times per week, ≥15–21 times per week, and ≥21 times per week), gas leakage (once per week and 1 to 3 times per month), and fecal incontinence among the vegetarians in this cohort should be considered unreliable due to the small sample size.

#### #Dietitians

#### Low-carbohydrate diets and mortality risk in Asian populations 🗷

In middle-aged and older Asian adults, adherence to a low-carbohydrate diet was not associated with mortality risk. However, adherence to plant-based low-carbohydrate diets was positively associated and adherence to meat-based low-carbohydrate diets was negatively associated with mortality risk.

#### Background

There is a lack of research that examines the links between long-term adherence to a *low-carbohydrate diet* (LCD) and mortality and also accounta for the quality and source of the carbohydrates.

#### The study

In this retrospective cohort study, the researchers used data from the Guangzhou Biobank Cohort Study

(GBCS)<sup>[335]</sup> to investigate the links between LCDs, as well as different types of LCDs (meat-based and plant-based), and the risk of all-cause, cancer, and *cardiovascular disease* (CVD) mortality in Asian populations. A total of 20,206 participants (ages ≥50) were included in the analyses.

The researchers used data from food frequency questionnaires to calculate the following diet scores:

- Overall LCD score: Calculated according to the percentages of energy from carbohydrate, fat, and protein
- Meat-based LCD score: Calculated according to the percentages of energy from low-quality carbohydrates (refined grains, added sugar, fruit juice, potatoes, and other starchy vegetables), animal protein, and saturated fat.
- Plant-based LCD score: Calculated according to the percentages of energy from high-quality carbohydrates (whole grains, whole fruits, legumes, and nonstarchy vegetables), plant protein, and unsaturated fat.

The researchers adjusted the analyses to account for the potential effect of confounding or mediating variables, including sex, age, socioeconomic factors, lifestyle factors, BMI, systolic blood pressure, total cholesterol, and fasting glucose.

#### The results

During an average duration of 15 years, 4,624 deaths occurred, including 1,534 from cancer, 1,783 from CVD, and 1,307 from other causes.

In the fully adjusted analyses, the overall LCD score was not associated with all-cause or cause-specific mortality. The highest ( compared to the lowest) quartile of plant-based LCD scores was associated with 16% and 39% higher risks of all-cause and CVD mortality, respectively. The highest (compared to the lowest) quartile of meat-based LCD scores was associated with 11% and 19% lower risks of all-cause and CVD mortality, respectively.

The results were similar when the analyses were restricted only to participants with diabetes.

#### **#Dietitians**

▲ Back to Table of Contents

## **Editor's Picks**

### Taking protein or amino acids postexercise might reduce inflammation and oxidative stress

#### Ø

This systematic review found that supplementation with protein or amino acids reduced postexercise inflammation or oxidative stress in some (but not most) studies. This inconsistency may be due to study heterogeneity, insufficient sensitivity (biomarker assessment), or insufficient power (study controls and analysis).

#### Background

Inflammation and *reactive oxygen species* (ROS) are necessary and important modes of signaling for muscle adaptation and regeneration, but they can also cause damage if left unchecked. Proper protein intake is crucial for recovery from exercise, and some animal studies suggest that protein has antioxidant and anti-inflammatory effects. Can it affect postexercise inflammation and oxidative stress in humans?

## • Digging Deeper: The balancing act of ROS and inflammatory signaling in muscle adaptation

Skeletal muscle generates ROS at rest, primarily from mitochondrial inefficiencies during energy metabolism. The neural and physical stress of muscle contraction during exercise, as well as the increased energy and oxygen demand, increase ROS production substantially, primarily from *reduced nicotinamide adenine dinucleotide phosphate* (NADPH) oxidase, an enzyme that mediates cell signaling and regulation of gene expression through the production of ROS.<sup>[6]</sup> Increased ROS levels alter the potential for the transfer of electrons between molecules (often referred to as redox potential) in muscles and can modify redox-sensitive proteins. If modified, redox-sensitive signaling pathways (e.g., nuclear factor erythroid 2-related factor 2, or nrf2) can activate various physiological responses/adaptations through regulation of gene expression (e.g., mitochondrial biogenesis via antioxidant response element activation).<sup>[7]</sup> Ideally, the exercise stress is enough to trigger an adaptive response (i.e., oxidative eustress) that promotes physiological changes, such as increasing mitochondria numbers to improve aerobic capacity, to prepare the body's response to another period of exercise stress in the future without purportedly causing too much damage that may prevent proper recovery. This damage could lead to overtraining and oxidative distress,

#### although there are likely other factors involved.<sup>[8][9][10]</sup>

At the same time, the increase in ROS and regulation of gene expression can signal the immune response of inflammation. While some factors may exert pro- or anti-inflammatory action, they generally signal muscle stress and damage and recruit a scavenger and recovery response to eliminate damaged cells and repair tissues.<sup>[11][12]</sup> ROS and inflammation can interact in a vicious cycle, depending on other stressors beyond exercise (e.g., smoking, disease, and aging), but within tolerable stress levels, ROS and inflammation serve as important signals for adaptation.



#### The study

This systematic review of 34 randomized controlled trials involved healthy adult participants (99% male, average age of 24) who underwent postexercise interventions consisting of whole protein (18 studies on whey, milk, etc.) or supplemental amino acid (16 studies on mixed amino acids, glutamine, taurine, etc.). The control interventions were flavored water, a carbohydrate beverage, or a sugar pill.

Study sample sizes ranged from 8 to 40 participants. Nineteen of the studies recruited trained athletes, 9 recruited recreationally active participants, and 6 recruited untrained participants.

Postexercise (less than 96 hours) markers of inflammation and oxidative stress included tissue sample levels of cytokines (e.g., interleukin-6, tumor necrosis factor-alpha), C-reactive protein, 8-hydroxydeoxyguanosine (an indicator of DNA damage), and total antioxidant capacity, among others.

#### The results

Most studies (20) did not demonstrate changes in postexercise levels of inflammatory or oxidative stress markers when compared to controls. Five studies on whole protein and 9 studies on supplemental amino acid interventions reported either anti-inflammatory or antioxidant effects in some markers when compared to controls.

#### Note

These results should be interpreted with caution for the following reasons:

- The study designs were very inconsistent, with varying doses, durations, whole protein or amino acid sources, and population characteristics.
- The intervention and diet were not always properly controlled, which could indirectly influence biomarkers of inflammation and oxidative stress.<sup>[13]</sup>
- Only a few biomarkers were measured in each study, and many can be very sensitive or dependent on the specific assay or sample used.<sup>[14][15]</sup>
- Several studies did not include these measurements as primary outcomes and were likely not sufficiently powered to detect differences.

#### The big picture

Protein's purported antioxidant effects are partially explained by its ability to enhance the availability of glutathione, a cofactor involved in the endogenous antioxidant response. It has also been shown to dampen inflammatory signaling, but the reports fueling these purported effects are primarily from animal and cell studies.<sup>[16][17]</sup> One human study that reported an antioxidant benefit involved a special carbohydrate and whey protein cake. In this case, not only does the combination with carbohydrate make it difficult to determine whether benefits were derived from the protein, carbohydrate, or both, but the participants also underwent "exhaustive cycling."<sup>[18]</sup> There may be more nuance to this relationship, such as the existence of an effect only following excess high-intensity exercise (or overtraining) that may trigger a high level of oxidative stress and oxidative distress.

There is also some controversy regarding whether antioxidant supplementation may interfere with redox signaling and blunt exercise-induced adaptation and recovery. A well-designed 11-week RCT from 2014 reported that supplementation with the antioxidants vitamins C and E decreased markers of exercise-induced cellular adaptation despite no difference in performance measures when compared to placebo.<sup>[19]</sup> A meta-analysis from 2020 reported that vitamin C and/or E supplementation that lasted more than 4 weeks did not influence aerobic or resistance training-induced adaptations in physiological

function.<sup>[20]</sup> A systematic review from 2022 reported that antioxidant supplementation before or during exercise can delay fatigue, reduce muscle damage, and decrease recovery time, <sup>[21]</sup> while a Cochrane systematic review from 2020 reported that antioxidant supplementation does not result in a clinically relevant reductions of muscle soreness.<sup>[22]</sup>

While novel, more precise tools are being developed to allow for a greater understanding of redox signaling and intricate cell communication, it appears that more research is needed to understand the subtlety in the relationship between exercise-induced ROS, adaptation, and protein supplementation. Since most of the underlying mechanisms involved in these relationships have been explored in animal models (some have yet to be proven) and studies are limited by various aspects of intervention (e.g., exercise duration, type, intensity), sample type (i.e., systemic vs. localized), measurement methods, and sensitivity (e.g., differences in hydration are not always monitored but can influence concentrations of analytes), the specifics are still being teased out.<sup>[7] [11][15]</sup> Alternatively, the null result may very well suggest that exercise-induced oxidative stress and inflammation are an important stimulus for muscle adaptation.

#### #EditorsPick, #SportsNutrition

#### Can a Mediterranean diet decrease liver fat without decreasing body weight?

In this 12-week randomized controlled trial, an ad libitum low-fat diet and Mediterranean diet similarly decreased liver fat and insulin resistance in adults with nonalcoholic fatty liver disease.

#### Background

*Nonalcoholic fatty liver disease* (NAFLD) is the most common cause of liver disease worldwide and affects about 25% of adults.<sup>[228]</sup> Diet and lifestyle interventions aimed at reducing body weight are the cornerstones of NAFLD treatment, as there are no approved medications for the condition. However, most people are unable to maintain substantial weight loss in the long term, which necessitates alternative treatment strategies. A *Mediterranean diet* (MedDiet) has demonstrated the potential to improve features of NAFLD without significant changes in body weight.<sup>[229][230]</sup>

#### The study

In this 12-week randomized controlled trial, 42 participants (average age of 52) with NAFLD and insulin resistance (43% of the participants had type 2 diabetes) were assigned to consume either a MedDiet or a *low-fat diet* (LFD). The LFD was based on the Australian Dietary Guidelines, which equated to about 30% of total energy from fat, 50% from carbohydrate, and 20% from protein. The MedDiet was based on a traditional Cretan diet, which equated to about 45% of energy from fat (more than 50% of which was monounsaturated fat), 35% from carbohydrate, and 20% from protein. There were no energy restrictions placed on either diet. Dietary adherence was assessed in face-to-face interviews using three-day food diaries at baseline, week 6, and week 12.
The primary outcome was liver fat measured by magnetic resonance spectroscopy. The secondary outcomes were *homeostatic model assessment for insulin resistance* (HOMA-IR), visceral fat (measured using bioelectrical impedance analysis), liver stiffness (measured using Fibroscan), markers of liver damage (*alanine aminotransferase* ALT, aspartate aminotransferase, *gamma-glutamyl transferase* GGT, and alkaline phosphatase), blood pressure, blood lipids, and *high-sensitivity C-reactive protein* (a marker of inflammation).



## The Mediterranean Diet pyramid

Adapted from Bach-Faig et al., Public Health Nutr., 2011.PMID:22166184

#### The results

Compared to baseline, there was a 17% reduction in liver fat in the LFD group and a borderline significant 8% reduction in liver fat in the MedDiet group. With respect to secondary outcomes, visceral fat decreased in both groups compared to baseline, with no difference between groups. There was a –1.0 point reduction in HOMA-IR in the LFD group and a *borderline significant* –0.5 point reduction in the MedDiet group, compared to baseline. Compared to the MedDiet group, ALT and GGT decreased in the LFD group. There were no significant changes in body weight in either group, which may have been due to the small

sample size, though body weight decreased by −3.5% in the LFD group, while body weight did not change in the MedDiet group.

## Note

The secondary outcomes should be considered exploratory because the researchers did not adjust for multiple comparisons despite the inclusion of numerous outcomes (which increases the risk of false-positive results), and the sample size was small.

At baseline, visceral fat and fasting plasma glucose were significantly higher in the LFD group than in the MedDiet group.

## The big picture

On the surface, the results of this trial suggest that a healthy LFD and a MedDiet are similarly effective for reducing liver fat and insulin resistance in adults with NAFLD. However, the results are more intriguing than they may seem. Clinically meaningful reductions in liver fat occurred in both groups without intentional caloric restriction (i.e., the diets were consumed *ad libitum*). Moreover, there was a clinically meaningful reduction without corresponding changes in body weight.

Weight loss generally reduces liver fat, so a hypocaloric diet alone or in conjunction with increased physical activity to produce a weight loss of at least 3–5% of body weight is recommended for people with NAFLD.<sup>[231]</sup> That said, it's unsurprising that liver fat decreased in the LFD group, considering there was an average body weight reduction of about 3.5%. In contrast, it is somewhat surprising that there was a clinically meaningful reduction in liver fat in the MedDiet group because there was no change in body weight.

In agreement with the findings of this study, other evidence suggests that a MedDiet reduces liver fat and improves cardiometabolic risk factors independent of changes in body weight. In a 6-week crossover trial published in 2013, participants with NAFLD consumed a MedDiet and a LFD.<sup>[229]</sup> There was a nonsignificant decrease in body weight with both diets (MedDiet: –1.0 kg vs. LFD: –2.4 kg). However, the decrease in liver fat was greater with the MedDiet than with the LFD (–39% vs. –7%), and insulin sensitivity improved with the MedDiet compared to baseline, while it did not change with the LFD.

In a randomized trial published in 2018, participants with NAFLD were assigned to either a MedDiet or a LFD for 12 weeks.<sup>[230]</sup> Similar to the above findings, there were notable reductions in liver fat (MedDiet: -32.4% vs. LFD: -25.0%) with nonsignificant changes in body weight (MedDiet: -2.1 kg vs. LFD: -1.6 kg), but the changes in liver fat were not significantly different between groups.

In these studies, most of the participants assigned to the MedDiet underwent a few significant dietary changes relative to their usual diet:

• Their monounsaturated fat intake increased.

- Their polyunsaturated fat intake increased, namely, omega-3 polyunsaturated fatty acids.
- Their saturated fat intake decreased.
- Their added sugar intake decreased.

Two randomized controlled trials have demonstrated that a diet high in monounsaturated fat substantially decreases liver fat in people with prediabetes or type 2 diabetes without changing body weight, compared to a high-fiber diet.<sup>[232][233]</sup> In addition, saturated fat seems to promote increases in liver fat, compared to polyunsaturated fat (mainly omega-6 polyunsaturated fatty acids),<sup>[234][235][236]</sup> and supplementing with omega-3 polyunsaturated fatty acids has been shown to reduce liver fat.<sup>[237]</sup> Lastly, a high intake of simple sugars, namely fructose, can increase liver fat independent of changes in body weight,<sup>[238][239]</sup> and restricting simple sugar intake effectively reduces liver fat.<sup>[240][241][242][243]</sup>

The most effective way to decrease liver fat is by consuming a hypocaloric diet and achieving a weight loss of at least 5% of body weight. However, evidence from mechanistic studies, observational studies, and randomized controlled trials demonstrate that the MedDiet and its individual components (e.g., olive oil, fatty fish, nuts, vegetables) have beneficial effects on features of NAFLD.<sup>[244]</sup> Therefore, transitioning from a Western diet rich in saturated fat and refined carbohydrates to a MedDiet has the potential to produce clinically meaningful reductions in liver fat without significant changes in body weight.

#Dietitians, #EditorsPick, #LiverDisease

## **Fat Loss**

## Are small changes the key to unlocking weight maintenance?

In this 3-year randomized controlled trial, small changes to diet and physical activity slightly decreased body weight over 3–15 months compared with the control, but there was no difference in body weight between groups at 18–36 months.

## Background

Modest weight gain (0.5–1.0 kilograms per year; kg) in adults who are overweight or obese is associated with an increased risk of certain cancers,<sup>[130]</sup> all-cause mortality,<sup>[131]</sup> and deterioration of health-related quality of life.<sup>[132]</sup> It's estimated that a reduction of about 100–150 kcal/day is required to prevent positive energy balance (i.e., taking in more calories than the body can burn) in most adults.<sup>[133]</sup> Could an approach focused on small changes to diet and physical activity improve long-term weight management?

## The study

This 3-year randomized controlled trial examined whether small changes in physical activity and diet could prevent weight gain in 320 participants (average age of 53) who were overweight or obese.

In phase I, the participants were assigned to either maintain their usual lifestyle (the control) or use the *small change approach* (SCA), which consisted of 17 group-based sessions and 9 individual counseling sessions (20 hours of contact total). The participants assigned to SCA were asked to increase their daily step count by 2,000, reduce their daily calorie intake by 100 kcal, and maintain these goals for the duration of the 2-year intervention. The participants in SCA also set weekly goals and developed a plan to maintain their small change goals. Additionally, the participants in SCA submitted dietary and physical activity logs and their SCA plan each week. Phase II was a 1-year passive follow-up period.

The primary outcome was change in body weight, which was assessed at baseline and 3, 6, 9, 12, 15, 18, 24, 30, and 36 months.

## The results

Body weight decreased 1.0 to 2.0 kg in SCA at 3, 6, 12, and 15 months, compared with the control group, but was no different between groups at 18, 24, 30, or 36 months.

Among participants who were overweight, weight gain was 2.4 kg and 2.2 kg less in SCA than in the control at 24 and 36 months, respectively. Among participants with obesity, body weight decreased in SCA compared with the control during the first year, but there was no difference between groups at 24 or 36 months.

## #Dietitians

## Do subnormal testosterone levels normalize after bariatric surgery in male adolescents?

This ancillary study found that in the 5 years after bariatric surgery and weight loss in male adolescents with severe obesity, total and free testosterone concentrations increased markedly.

#### Background

Obesity in both male adolescents and adults is negatively associated with testosterone concentrations. Importantly, research suggests that testosterone concentrations improve markedly following bariatric surgery in adult men with obesity. Therefore, it is possible that a similar improvement may be observed in male adolescents with obesity. This study explored this possibility.

#### The study

This was an ancillary study based on data from the (Teen-LABS) study,<sup>[249]</sup> a prospective cohort study that enrolled adolescents with severe obesity who were undergoing bariatric surgery.

In the ancillary study, the researchers examined the changes in a number of hormones in 34 male participants (ages 14–20) from the Teen-LABS study over a period of up to 5 years after bariatric surgery.

The hormones measured were total testosterone, free testosterone, estradiol, *sex hormone-binding globulin* (SHBG), *luteinizing hormone* (LH), and *follicle-stimulating hormone* (FSH).

#### The results

On average, the study participants lost one-third of their body weight after bariatric surgery. Maximum weight loss was achieved by year 1, with a slight regain noted between years 2 and 3.

Total testosterone increased from 6.7 nmol/L (below the normal range) to 17.6 nmol/L (within the normal range) at 2 years and to 13.8 nmol/L (within the normal range) at 5 years. Before surgery, 79% of the participants had subnormal total testosterone levels. At 2 and 5 years after surgery, only 15% and 22%, respectively, of the participants had subnormal total testosterone levels.

Similarly, free testosterone increased from 0.17 nmol/L (below the normal range) to 0.34 nmol/L (within the normal range) at 2 years and to 0.27 nmol/L (within the normal range) at 5 years. Before surgery, 73% of the participants had subnormal free testosterone levels. At 2 and 5 years after surgery, only 20% and 33%, respectively, of the participants had subnormal free testosterone levels.

## #Dietitians, #Obesity

## The effect of a short-term low-fiber diet on body mass 🗷

In this noncontrolled trial, healthy men consumed their usual diet for 7 days and then decreased their fiber intake by 23 grams per day for 4 days. The low-fiber diet decreased body mass by 0.58 kilograms.

## Background

Body mass is frequently manipulated by athletes involved in weight-sensitive sports (e.g., combat sports, weightlifting) in an attempt to gain a competitive advantage over their opponents. For example, reducing body mass allows athletes to compete in lower weight categories against opponents with short limb lengths and lower power-to-body-mass ratios. Acute alterations in dietary fiber intake can reduce body mass by reducing the mass of undigested fiber, bacteria, and water retained in the intestines. However, a study had yet to quantify the extent to which low-fiber diets can reduce body mass in the short term.

#### The study

In this 12-day noncontrolled trial, 19 healthy, physically active men (average age of 32) consumed their habitual diet (HAB; about 30 grams of fiber per day) for 7 consecutive days and then switched to a low-fiber diet (LOW; < 10 grams of fiber per day) that was matched for energy, macronutrient, fluid, and sodium content for 4 consecutive days. Daily exercise load was also matched between conditions.

The primary outcomes were body mass (measured daily upon waking and after first urination using a digital scale provided by the research staff) and dietary intake (measured using the remote food photography method). The secondary outcomes were appetite (measured using a 100-point visual analog scale), stool type (measured using the Bristol Stool Scale Form), and stool frequency.

#### The results

Body mass was similar on days 1–3 of HAB and LOW. However, body mass was decreased in LOW compared to HAB on days 4 and 5. On average, body mass decreased by 0.58 kilograms (0.74%) during LOW. Thus, it takes about three days for detectable changes in body mass to occur when eating a low-fiber diet.

Stool frequency decreased from twice per day during HAB to once per day during LOW. Additionally, stool hardness increased on days 3 and 4 of LOW compared to HAB. Subjective hunger increased and fullness decreased in LOW compared to HAB.

#### Note

A limitation of this study was that meals were not provided to the participants during LOW. Although there were no reported differences in energy, macronutrient, sodium, or fluid consumption between conditions, there may have still been measurement errors by the participants that influenced body mass changes.

Also, because only men were included, the results are not necessarily generalizable to women, who may have slower gastrointestinal motility.<sup>[252]</sup>

## #SportsNutrition

## 👎 Gut Health

## Vitamin D supplementation for people with IBS 🗷

In this meta-analysis, vitamin D supplementation improved the severity of irritable bowel syndrome symptoms, but only when trials with moderate or high risk of bias were included in the analysis.

## Background

According to observational research, there is a high prevalence of vitamin D deficiency in individuals with *irritable bowel syndrome* (IBS). However, it's unclear whether supplementation with vitamin D can improve the severity of IBS symptoms.

#### The study

This meta-analysis of 8 randomized controlled trials examined the effects of supplementation with vitamin D, compared to placebo, on IBS symptom severity (8 trials) and quality of life (4 trials) in 685 total participants with IBS.

The trials were conducted in Iran, Egypt, and the United Kingdom. The average age of the participants ranged from 16 to 41 years. In 4 trials, vitamin D was taken as a bolus dose of 50,000 IU twice per week, once per week, or every 2 weeks. In the other 4 trials, vitamin D was taken daily, with the dose ranging from 2,000 to 4,000 IU.

## The results

In the main analyses, vitamin D supplementation improved IBS symptom severity to a small degree but did not affect quality of life.

In a subgroup analysis that excluded 1 trial published in a predatory journal, the effect of vitamin D on IBS symptom severity remained statistically significant. However, when only trials with a low risk of bias were included in the analysis, the effect became statistically insignificant.

#### Note

Predatory journals are journals that typically charge the authors publication fees without providing robust peer review or editorial services.<sup>[334]</sup>

## #Dietitians

## Healthy Aging & Longevity

## Exercise, mitochondria, adipose tissue, and aging 🗷

This cross-sectional study found that lifelong high-volume exercise training can ameliorate losses in the mitochondrial function of adipose tissue that occur with aging.

## Background

Physiological function and metabolism gradually degrade as people age. Age influences mitochondria, which are the powerhouses of cells, and white adipose tissue, which is a key organ in energy balance and whose metabolism is mediated by mitochondrial function. This influence is particularly interesting because exercise training can improve mitochondrial health. Can lifelong exercise prevent age-associated losses in the mitochondrial function of adipose tissue?

## The study

This cross-sectional study recruited 20 healthy and untrained men (10 with an average age of 26 and 10 with an average age of 67) and 12 older, healthy, and lifelong-trained men (average age of 69). The latter group was further divided into moderately trained (6 participants) and highly trained (6 participants) according to the exercise endurance test results.

The lifelong-trained participants self-reported that they performed ≥ 2 hours of endurance exercise training per week starting from late adolescence. Participant health status was verified by a medical doctor's review of electrocardiography results and blood glucose, lipoprotein, and C-reactive protein measures within normal reference ranges.

Exercise performance was evaluated by an incremental exercise test using a bicycle ergometer. Body composition was measured by DXA. On a separate day, fasting blood samples and biopsies of abdominal *subcutaneous white adipose tissue* (sWAT) and muscle tissue were obtained to measure markers of oxidative capacity (e.g., adiponectin, tumor necrosis factor-alpha, hydrogen peroxide) and mitochondrial health (e.g., respiratory capacity, turnover).

## The results

Overall, mitochondrial respiratory capacity was lower in sWAT from older participants, compared to younger participants. However, mitochondrial respiratory capacity (attributed to higher mitochondrial content rather than improved efficiency) and markers of oxidative capacity were higher in sWAT from lifelong *highly* trained participants than all other groups.

## #Dietitians, #SportsNutrition

## Fruits, vegetables, nutrients, and arthritis 🛛

This cross-sectional study reports that an increased intake of micronutrients, fruits, and green vegetables is associated with a decreased risk of arthritis and osteoarthritis in older participants.

## Background

Arthritis is associated with *cardiovascular disease* (CVD). A reduced risk of CVD is associated with fruit and vegetable intake, a healthy diet, and both intake and blood concentrations of antioxidants. <sup>[111][112][113]</sup> Is greater fruit, vegetable, and micronutrient intake also associated with a reduced arthritis risk?

## The study

This cross-sectional study involved 33,966 participants (average age of 64; 50% male) who completed the Korea National Health and Nutrition Examination Survey between 2009 and 2019.

Diagnosis of arthritis, *osteoarthritis* (OA), or rheumatoid arthritis by a physician was self-reported. Covariates, such as demographics and anthropometrics (body measurements), and comorbidities (e.g., hypertension and depression) were obtained from medical checkups.

The participants estimated their daily intake of fruits, green vegetables, and other vegetables with a food frequency questionnaire and were divided into three groups by consumption: low, moderate, and high. Nutrient intake was estimated from a 24-hour recall.

The researchers analyzed urinary cotinine (a metabolite of nicotine) to verify smoking status (smoking is strongly associated with arthritis) and used the Framingham risk equation (based, by sex, on cholesterol concentrations, blood pressure, age, and smoking) to estimate the 10-year risk of CVD.

## The results

The nearly 25% of participants who had arthritis or OA were more likely to be female, older, unemployed, and drinkers; participate in less physical activity; consume fewer micronutrients; and have poorer levels of cardiometabolic health markers.

Participants who consumed two times the amount of vitamins B<sub>1</sub> and B<sub>2</sub>, polyunsaturated fats, and omega-3s daily showed a 7% lower risk of arthritis and OA (following adjustment for confounders).

Participants with arthritis were 28% and 26% more likely to consume a low amount of fruits and green vegetables, respectively; participants with OA were 30% more likely to consume a low amount of fruit.

Compared with lower CVD risk, a higher risk of CVD was associated with a 26% and 24% increased prevalence of arthritis and OA, respectively,.

## Note

These results should be interpreted with caution due to the observational nature of the study, the use of

self-reported data, and the large number of variables involved in the analysis.

## #Dietitians

## Polygenic risk scores, fruit and vegetable intake, and cognitive decline 🛛

This cohort study found that <5 fruit and vegetable servings per day is associated with a 33–37% greater risk for dementia diagnosis. The increase in risk may be enhanced in the context of polygenic predisposition to Alzheimer's disease, schizophrenia, and general cognitive changes.

## Background

*Polygenic risk scores* (PGS) are used to summarize the genetic predisposition for a certain trait or health condition. Greater *fruit and vegetable* (FV) intake has been associated with a reduced risk of cognitive decline. Can PGSs for cognitive decline and daily FV intake be combined to better evaluate the risk of dementia diagnosis?

## The study

This cohort study involved 6,784 participants (average age of 65; 46% male) from the English Longitudinal Study of Aging during an average follow-up period of 10 years.

The PGS for Alzheimer's disease, schizophrenia, and general cognition were calculated using summary statistics from genome-wide association studies. The diagnosis of dementia was determined by self-reported physician diagnosis or from IQCODE (Informant Questionnaire on Cognitive Decline) assessment.<sup>[184]</sup>

FV intake was estimated by asking participants how many small glasses of fruit juice, tablespoons of fruits and/or vegetables, or how much salad (using a cereal bowl as the standard for measurement) was eaten. The data were categorized into a binary variable (i.e., ≥5 or <5 FV servings per day) based on the World Health Organization's recommendations to consume ≥5 servings of FVs per day.

Sex and genetic ancestry (including APOE-ε4, a strong genetic risk factor for Alzheimer's disease)<sup>[185]</sup> were included as covariates in the analyses.

## The results

Overall, a total of 175 participants (4%) were diagnosed with dementia. The consumption of <5 FV servings/day was associated with a 33–37% greater risk for dementia diagnosis (depending on the genetic predisposition). A higher PGS for Alzheimer's disease was associated with a 24% greater risk of dementia diagnosis and a 47% greater risk of Alzheimer's disease diagnosis.

A multiplicative interaction (a combined effect that is larger than the product of the individual effects) was observed between greater PGS for schizophrenia and intake of <5 FV servings/day, resulting in a 66% increased risk of Alzheimer's disease diagnosis.

A higher PGS for general cognition was associated with a reduced risk (20%) for non-Alzheimer's disease diagnosis. There was also an additive interaction between PGS for general cognition and <5 FV servings/ day in association with Alzheimer's disease diagnosis.

#### Note

These results should be interpreted with caution for several reasons:

- They could be subject to the multiple comparisons problem (i.e., with the many analyses conducted, so many variables were involved in the PGS, dietary assessment and covariates that the chance of finding an association by chance is high).
- The diagnostic accuracy of the IQCODE tool for dementia diagnosis is still debated.<sup>[184]</sup>
- The method of dietary assessment is rather different from the commonly used tools (i.e., the accuracy of estimated serving sizes is debatable; how does a tablespoon of intake equate to servings?), and it was only employed for baseline daily intake and only for the previous day, not an average day.
- The PGS are based on the availability of certain data from genome-wide studies that are often conducted on a certain demographic and thus may not be representative of the general population.

#Dietitians, #AlzheimersDisease

# Herbal Supplements

## Pomegranate-rind and cocoa-seed extracts for increasing testosterone

A proprietary blend of extracts from pomegranate rind and cocoa seeds increased total and free testosterone levels in healthy young men.

#### Background

Limited evidence from preclinical research suggests that extracts from the rind of *Punica granatum L*. (commonly known as pomegranate) and the seeds of *Theobroma cacao L*. (commonly known as cocoa) may increase the production of steroid hormones. Can supplementation with Tesnor™ (a proprietary blend containing pomegranate-rind and cocoa-seed extracts in a 4:1 ratio) increase testosterone levels in healthy young men?

#### The study

In this 56-day randomized control trial, 119 healthy men ages 21–35 who were not performing resistance training were assigned to one of three groups:

- 1. Low dose: The participants took capsules containing 200 milligrams (mg) of Tesnor after breakfast.
- 2. High dose: The participants took capsules containing 400 milligrams of Tesnor after breakfast.
- 3. Placebo: The participants took capsules containing a placebo after breakfast.

The participants were asked to maintain their regular diets, refrain from consuming any other nutritional supplements or energy drinks, and perform 40 minutes of aerobic exercise per day, 4 days per week, during the study.

The primary outcomes were the serum levels of total testosterone and free testosterone. The secondary outcomes were the serum levels of the hormones dihydrotestosterone, cortisol, luteinizing hormone, and estradiol. Handgrip strength and mid–upper arm circumference were also measured. Blood pressure, pulse rate, respiratory rate, temperature (taken orally), and a number of urinary and blood clinical parameters were assessed to determine the safety of the product.

#### The results

After 56 days, total testosterone levels increased more with high-dose Tesnor (+18.9%) than with placebo (+2.4%). Free-testosterone levels increased more with both high-dose (+25.3%) and low-dose (+13.7%) Tesnor than with placebo (+3.2%). Compared with placebo, luteinizing hormone levels increased only in the high-dose group.

Handgrip strength increased more with both high-dose and low-dose Tesnor than placebo, while mid–upper arm circumference increased more than placebo with high-dose Tesnor only.

There were no differences in any of the safety parameters.

#### Note

The trial was exploratory, so the findings should be considered preliminary. It's also worth noting that the study was funded by Laila Nutraceuticals, the manufacturer of Tesnor.

## #Dietitians

## Ginger and liver health 🗵

This meta-analysis of animal studies and qualitative review of human trials found some evidence that ginger supplementation can improve markers associated with liver health.

## Background

Ginger has anti-inflammatory and antioxidant properties and can improve blood lipids. Is it beneficial for fatty liver?

## The study

This systematic review and meta-analysis of 17 animal studies assessed the effects of ginger supplementation on the following outcomes:

- Alanine aminotransferase (ALT, a liver enzyme; lower levels are optimal)
- Aspartate aminotransferase (AST, a liver enzyme; lower levels are optimal)
- Catalase (an enzyme with antioxidant properties; higher levels are optimal)
- Free fatty acids
- HDL-C
- LDL-C
- Malondialdehyde (a marker of oxidative stress; lower levels are optimal)
- Superoxide dismutase (an enzyme with antioxidant properties; higher levels are optimal)
- Total cholesterol
- Triglycerides

In addition, the authors qualitatively analyzed 3 studies conducted on humans.

## The results

In the quantitative analysis of animal studies, ginger improved *liver* levels of the following:

- Cholesterol (-5.60 mg/g)
- Triglycerides (-4.08 mg/g)

Ginger also improved *serum* levels of the following:

- ALT (-2.85 U/L)
- AST (-0.98 U/L)
- Catalase (+3.35 nmol/mg),
- Fasting blood sugar (-2.53 mg/dL)
- HDL-C (+1.27 mg/dL)
- LDL-C (-3.94 mg/dL)
- Malondialdehyde (-3.16 nmol/L)
- Superoxide dismutase (+3.01 U/mg),
- Triglycerides (-4.98 mg/dL)
- Total cholesterol (-3.35 mg/dL)

The qualitative analysis of 3 clinical trials in humans found the following:

- In a 2016 randomized controlled trial, 44 patients with *nonalcoholic fatty liver disease* (NAFLD) consumed 2 grams per day of ginger or a placebo for 12 weeks. Ginger reduced serum ALT and gamma-glutamyl transferase levels (another marker of liver health) compared to placebo. There was no effect of ginger on liver fibrosis or AST.<sup>[122]</sup>
- In a 2020 randomized controlled trial, 46 patients with NAFLD were randomized to take 1.5 grams of ginger per day or a placebo for 12 weeks. Serum levels of ALT, total cholesterol, LDL-C, fasting blood sugar, HOMA-IR, C-reactive protein, and fetuin-A were lower in the ginger group than the placebo group. There were no differences between the two groups in body weight, fasting insulin, HDL-C, triglycerides, gamma-glutamyl transferase, AST, adiponectin, TNF-α, total antioxidant capacity, hepatic steatosis, or blood pressure.<sup>[123]</sup>
- In a 2021 randomized controlled trial, 46 active men were randomized to i) take 3 grams per day
  of ginger and perform *high-intensity interval training* (HIIT), ii) take 3 grams of ginger without
  performing HIIT, iii) perform HIIT without taking ginger, or iv) take neither ginger nor perform HIIT
  for 4 weeks. The group that took ginger and performed HIIT had greater improvements in HOMA-

IR, ALT, AST, blood glucose, insulin, body weight, waist circumference, and BMI than the other groups<sup>[124]</sup>

#Dietitians, #LiverDisease

## Immunity & Infectious Disease

## Vitamin D reduces flu risk 🛛

A meta-analysis of 10 randomized controlled trials reports that supplementation with vitamin D reduces the risk of flu by 22%.

## Background

Vitamin D deficiency has been associated with an increased incidence of respiratory tract infections and influenza, but supplementation studies have been inconsistent.

## The study

This meta-analysis of 10 randomized controlled trials included 4,859 participants (ages 3 months to 82 years) who took a vitamin D supplement (500–6,800 IU per day of oral cholecalciferol; 400 IU/day for infants and young children) or a placebo for 1–18 months. The participants were monitored for flu infection.

#### The results

Supplementation with vitamin D reduced the risk of flu infection by 22%, and heterogeneity (variability in data) among the included studies was low. There was no evidence of a risk of publication bias, and sensitivity analyses suggest a robust result.

## **#Dietitians**

## Is zinc or vitamins C or D linked to COVID-19 outcomes?

In this meta-analysis, supplementation with vitamin D, but not vitamin C or zinc, was associated with a reduction in intubation rate in individuals with COVID-19.

#### Background

Some observational studies have found links between low serum levels of some micronutrients (including vitamin C, vitamin D, and zinc) and worse COVID-19 outcomes. However, it's unclear whether supplementation with these individual micronutrients can improve clinical outcomes in individuals with COVID-19.

#### The study

This meta-analysis of 26 studies (10 randomized controlled trials and 16 observational studies) examined the links between individual supplementation with vitamin C, vitamin D, or zinc and clinical outcomes in a total of 5,633 individuals with COVID-19. Micronutrient supplementation was compared to standard care. The primary outcome was mortality, and the secondary outcomes were intubation rate and length of hospital stay.

Vitamin C supplementation was examined in 9 studies involving 1,488 individuals. The studies were conducted in China, the United States, Iran, Saudi Arabia, Pakistan, and Turkey. Vitamin C was given intravenously in 7 studies at dosages ranging from 50 milligrams to 24 grams per day and orally in 2 studies in dosages of 1 or 8 grams per day. The treatment duration ranged from 4 to 18 days.

Vitamin D supplementation was examined in 13 studies involving 3,497 individuals. The studies were conducted in Spain, France, India, Italy, Brazil, the United States, and Turkey. Vitamin D was taken before COVID-19 diagnosis in 4 studies, after COVID-19 diagnosis in 8 studies, and both before and after COVID-19 diagnosis in 1 study. The dose and treatment duration were highly variable across studies.

Zinc supplementation was examined in 5 studies involving 738 individuals. The studies were conducted in the United States, Australia, Egypt, and Saudi Arabia. Zinc was given orally in 4 studies as sulfate or gluconate in dosages ranging from 7 to 50 milligrams of elemental zinc per day and intravenously as chloride in 1 study at 0.5 milligrams per kilogram of body weight per day. The treatment duration ranged from 7 to 15 days.

## The results

None of the 3 micronutrients were associated with changes in mortality or the length of hospital stay. Vitamin D, but not vitamin C or zinc, was associated with a lower intubation rate.

Of the 26 studies, 23 had a low risk of bias, and 3 had a high risk of bias.

## **#Dietitians**

# Infants, Children & Teenagers

## Omega–3s improved maternal health and birth outcomes 🗷

This meta-analysis found that supplementation with omega–3s during pregnancy increased gestation by 1.4 days and birth weight by 49 grams. It also reduced the risks of preeclampsia (–16%), preterm delivery (–14%), and early preterm delivery (–23%).

#### Background

Some evidence suggests that supplementation with omega-3 fatty acids during pregnancy may have beneficial effects on both maternal health and birth outcomes. What does the totality of the available clinical evidence say?

## The study

This meta-analysis of 59 randomized and quasi-randomized controlled trials examined the effects of supplementation during pregnancy with omega–3s (i.e., docosahexaenoic acid and/or eicosapentaenoic acid and/or alpha-linolenic acid; aka DHA, EPA, and ALA), compared to placebo or no intervention, on a number of maternal health and birth outcomes.

The primary outcomes were the following:

- Incidence of pregnancy-induced hypertension (11 trials)
- Incidence of preeclampsia (24 trials)
- Gestational duration (46 trials)
- Incidence of preterm delivery (<37 weeks; 27 trials)
- Incidence of early preterm delivery (<34 weeks; 12 trials)
- Newborn birth weight (37 trials)
- Low newborn birth weight (14 trials)
- Newborn length (31 trials)
- Newborn head circumference (26 comparisons)

The secondary outcomes were the following:

- Risk of admission to the neonatal intensive care unit (13 trials)
- Incidence of cesarean delivery (29 trials)

- Prenatal death (12 trials)
- Infant death (10 trials)

## The results

Supplementation with omega–3s reduced the risk of preeclampsia by 16%, increased gestational duration by 1.4 days, increased newborn birth weight by 49 grams, and reduced the risk of preterm and early preterm delivery by 14% and 23%, respectively.

The risk of bias was low in 29 trials, moderate in 19 trials, and high in 11 trials.

## #Dietitians

## Sugar and sleep in school children – is there a relationship? 🗷

Children who often consume sugar-sweetened beverages were more likely to sleep less than children with a low sugar-sweetened beverages intake, but only on school days. This association was not found on weekends.

## Background

*Sugar-sweetened beverages* (SSB) may interfere with children's sleep patterns (e.g., sleep duration and sleep debt), and such sleep alterations are associated with lower cognitive performance<sup>[214][215]</sup> and a higher risk of obesity.<sup>[216]</sup> A 2018 cross-sectional study of 5,873 children ages 9–11 found that frequent consumption of SSB was associated with lower sleep duration,<sup>[217]</sup> and the participants often did not meet the sleep duration of 9–12 hours per night recommended by the American Academy of Sleep Medicine.<sup>[218]</sup>

However, the 2018 study did not account for school days or weekends and did not investigate sleep debt — an alternative measure of sleep quality.<sup>[219][220][221][222]</sup> The current study examined the association between children's SSB intake and sleep quality while accounting for school days and weekends.

## The study

This cross-sectional study of 2,628 Taiwanese children (ages 6–12) investigated the association between the frequency of SSB intake and sleep quality (assessed in terms of sleep duration and sleep debt). The researchers extracted the frequency of SSB intake from food frequency questionnaires and divided the cohort into low and high SSB intake groups.

Sleep duration was derived from 3-day physical activity logs. Sleep debt was defined and calculated as the difference in sleep duration on weekends and school days.<sup>[219][220][221][222]</sup>

The researchers also controlled for age, sex, and demographic variables and investigated the effect of caffeine content and BMI as confounding factors.

## The results

On average, the children slept for 8.8 hours on school days and 9.7 hours on weekends, yielding a sleep debt of 0.9 hours. With increasing age, sleep duration on school days (but not on weekends) further decreased (from 9.4 hours to 8.3 hours at 6 and 12 years of age, respectively), while sleep debt steadily increased (from 0.2 hours to 1.3 hours at 6 and 12 years of age, respectively).

For SSB consumption, children in the high intake group slept less than those in the low intake group, but only on school days. In contrast, weekend sleep duration was not significantly different. Consequently, children in the high SSB intake group also experienced greater sleep debt than those in the low intake group.

These effects remained even after adjusting for sex, age, and demographic variables. Also, sleep duration was not influenced by BMI or the caffeine contents of the SSB.

#### Note

This study has two important limitations. First, due to the cross-sectional design, the study cannot infer a causal relationship between the frequency of SSB intake and sleep duration. Second, the current study measured only the frequency, but not the surplus energy intake, of children's SSB consumption, similar to previous cross-sectional studies.<sup>[217]</sup>

#### #Dietitians, #SleepImpairment

## Is high-dose vitamin D supplementation safe in young children?

High-dose vitamin D supplementation in children (ages 0–6) was not associated with an increased risk of adverse events.

#### Background

According to the European Food Safety Authority, the tolerable upper intake levels of vitamin D are 1,000 IU/day for infants aged 0–6 months, 1,400 IU/day for infants aged 6–12 months, and 2,000 IU/day for children aged 1–10 years.<sup>[336]</sup> That said, there is a lack of evidence from meta-analyses on the safety of high-dose vitamin D supplementation in early childhood.

#### The study

This meta-analysis of 21 randomized controlled trials examined the associations between high-dose vitamin D supplementation (>1000 IU/day), compared to low-dose vitamin D supplementation (≤400 IU/day) or a placebo, and the risk of adverse events in a total of 7,358 children aged 0–6 years.

The types of adverse events examined were serious adverse events (death or hospitalization) and hypercalcemia (abnormally high blood levels of calcium). The daily dose of vitamin D ranged from 1,200 to 10,000 IU, whereas bolus doses ranged from 30,000 IU/week to 600,000 IU (given as a single dose). Most

studies listed a clinical diagnosis or vitamin D deficiency as inclusion criteria.

## The results

No association was detected between high-dose vitamin D supplementation and the risk of serious adverse events or hypercalcemia.

## #Dietitians

## 📂 Liver Health

## Vitamin C intake, liver function, and glucose metabolism 🗷

This cohort study found a linear association between i) dietary vitamin C intake and ii) liver function and glucose metabolism.

## Background

*Nonalcoholic fatty liver disease* (NAFLD) is characterized by the infiltration of liver cells with fat and is associated with cardiometabolic disease, oxidative stress, and inflammation.<sup>[176][177]</sup> Beyond its role in tissue repair, collagen formation, and other processes, vitamin C is an antioxidant with a suggested role in the regulation of hepatic and circulating lipid homeostasis; can it improve liver function?

#### The study

This cohort study included data from 8,307 participants (average age of 50; 47% male) from the 2009 China Health and Nutrition Survey.

Dietary vitamin C intake was estimated from 3-day 24-hour dietary questionnaires. The participants were divided into quartiles based on their dietary vitamin C intakes. Fasting blood plasma biomarkers of liver function and glucose and lipid metabolism were measured.

The analyses were adjusted for dietary vitamin C intake, age, gender, BMI, residence (i.e., urban vs. rural), and smoking status.

#### The results

Overall, about 25% of participants consumed inadequate levels of vitamin C (i.e., less than the estimated average requirement of 85 milligrams per day).

Higher vitamin C intake was associated with lower concentrations of plasma ferritin (an independent indicator of tissue damage and fibrosis in NAFLD)<sup>[178]</sup> and HbA1c (biomarker of glucose metabolism) and higher albumin (an indicator of a healthy liver).

Interestingly, higher vitamin C intake was also positively associated with the percentage of male participants and urban residence. No changes in lipid metabolism were found.

#### Note

These results should be interpreted with caution because of the observational nature of the study, the reliance on self-reported data, and the lack of plasma vitamin C concentration monitoring.

#### **#Dietitians**

## ALT and metabolic associated fatty liver disease in an Australian cohort 🗷

Elevated alkaline phosphatase and metabolic associated fatty liver disease were present in 13% and 37%, respectively, of this Australian cohort. Participants with elevated alanine aminotransferase were 3.57 times more likely to have metabolic associated fatty liver disease than those without elevated alanine aminotransferase.

## Background

*Metabolic associated fatty liver disease* (MAFLD), also known as *nonalcoholic fatty liver disease* (NAFLD), is a condition in which the liver accumulates excessive fat due to reasons other than alcohol use. Elevated *alanine aminotransferase* (ALT) levels can indicate fatty or cirrhotic liver and often occur among individuals with MAFLD, obesity, or metabolic syndrome.

## The study

This cross-sectional study assessed the prevalence of ALT elevation and MAFLD among 4,747 Australian adults in 2012. As secondary outcomes, the authors also identified factors independently associated with elevated ALT and assessed the proportion of participants with MAFLD who were at risk of advanced fibrosis.

The authors performed liver function tests and assessed BMI, waist circumference, blood pressure, blood lipids, oral glucose tolerance tests, and HbA1C. MAFLD was defined as hepatic steatosis (determined using the Fatty Liver Index) alongside a BMI ≥25, the presence of *type 2 diabetes* (T2D), or at least two metabolic risk factors.

The BARD score (BMI  $\geq$  28 = 1 point, AST/ALT ratio of  $\geq$ 0.8 = 2 points, type 2 diabetes = 1 point) was used to identify participants with MAFLD who were at risk of advanced fibrosis (a score of  $\geq$ 2 is associated with advanced fibrosis).

## The results

Elevated ALT was present in 13% of the total participants, 22% of participants with diabetes, 18% of those with obesity, and 17% of those with metabolic syndrome. Female gender, higher diastolic blood pressure, elevated triglycerides, T2D, a sedentary lifestyle, and a high waist circumference were all independently associated with elevated ALT.

MAFLD was present in 37% of the cohort. Male gender, older age, T2D, low HDL-C, high diastolic blood pressure, a sedentary lifestyle, and not completing any postsecondary education were all independently associated with MAFLD.

Participants with elevated ALT were 3.57 times more likely to have MAFLD than those without elevated ALT. Of the participants with MAFLD, 61% had a BARD score ≥2.

## #Dietitians, #LiverDisease

## Do dietary patterns modify the risk for diabetes among people with NAFLD? 🗷

In this cohort study, a high intake of vegetables, eggs, soy, and coarse cereals reduced the risk of type 2 diabetes among people with nonalcoholic fatty liver disease.

## Background

*Nonalcoholic fatty liver disease* (NAFLD) is a risk factor for *type 2 diabetes* (T2D). However, it's unclear whether dietary patterns can modulate this effect.

## The study

This prospective cohort study of 24,602 participants in China assessed whether dietary patterns could modify the risk for T2D among patients with NAFD. As a secondary outcome, the authors assessed the effect based on BMI (<25 or ≥25).

NAFLD was diagnosed using liver ultrasonography. Dietary intake (including alcohol intake, to differentiate NAFLD from alcoholic fatty liver disease) was assessed using a food frequency questionnaire. Incident T2D was assessed via fasting blood samples. The authors controlled for the following confounding variables:

- Age
- BMI
- Drinking status
- Education level
- Employment status
- Energy intake
- Household income
- Hyperlipidemia
- Hypertension
- Physical activity
- Sex
- Smoking status
- Waist circumference
- Family history of cardiovascular disease, hypertension, and diabetes
- Dietary pattern other than the intake pattern assessed  $\xi$

The authors classified the participants based on whether they were above or below the median intake of three dietary patterns:

- Animal foods (animal organs/blood, meat, processed meat products, and preserved eggs)
- Fruit/sweet foods (fruits, cakes, and ice cream)
- Vegetables/eggs/other plant foods (vegetables, eggs, soy, and coarse cereals)

## The results

Over an average follow-up period of 3.8 years, 787 (3.2%) participants developed type 2 diabetes. After adjusting for confounders, compared to participants without NAFLD, patients with NAFLD had a 3x greater risk of developing T2D.

After adjusting for confounders (other than intake of vegetables/eggs/other plant foods), participants with NAFLD and a low intake of vegetables/eggs/other plant foods had a 4x greater risk of T2D than participants without NAFLD. In contrast, participants with NAFLD and an above-the-median intake of vegetables had a 2–3x greater risk for T2D. There were no associations between intake of fruit/sweet foods or animal foods and T2D risk.

When the authors further stratified the participants by BMI (<25 or ≥25), high vegetable intake reduced the risk for T2D for participants with NAFLD in both BMI categories.

## Note

<sup>§</sup>Adjustment of each dietary pattern for other dietary patterns:

- In the vegetable/egg/other plant food analysis, the researchers adjusted for fruits/sweet foods and animal foods.
- In the fruits/sweet foods analysis, they adjusted for vegetable/egg/other plant foods.
- In the animal food analysis, they adjusted for vegetable/egg/other plant foods and fruit/sweet food intake.

## #Dietitians, #LiverDisease

## L-ornithine L-aspartate for hepatic encephalopathy

Patients with overt hepatic encephalopathy (a liver-related disorder of the nervous system) who received Lornithine L-aspartate alongside standard treatment demonstrated greater improvements than patients who received standard treatment alone.

## Background

Overt hepatic encephalopathy (OHE) is a brain impairment caused by the liver's failure to remove

ammonia and other toxins. People with OHE have a wide range of symptoms such as personality changes, lethargy, confusion, and coma.<sup>[250]</sup>

*L-ornithine L-aspartate* (LOLA) is often used alongside other agents such as lactulose and rifaximin to reduce ammonia levels in these individuals. This trial compared the effects of intravenous LOLA to a placebo in 140 hospitalized patients with cirrhosis and grade III-IV OHE.

## The study

The 140 patients in this randomized controlled trial were randomized to receive intravenous LOLA or a placebo, with both groups also receiving lactulose and rifaximin. LOLA was provided as a continuous intravenous infusion at a dosage of 30 grams daily for five days. Both groups received rifaximin through a nasogastric tube and lactulose either orally or through a nasogastric tube. All patients also received general treatment for cirrhosis with OHE. After five days, patients who did not demonstrate an improvement received standard-of-care treatment and were counseled for a liver transplant.

The primary outcome was an improvement in OHE, defined as an improvement by at least two grades of OHE severity. The secondary outcomes were changes in blood ammonia and serum cytokines, rates of mortality and recovery, and the length of hospital stay.

## The results

The LOLA group experienced a higher rate of improvement in OHE (92.5% vs. 66%), greater reductions in ammonia, IL-6, and TNF- $\alpha$ , a shorter time to recovery (2.7 vs. 3 days), and a lower 28-day mortality (16.4% vs. 41.8%) than the placebo group. Both groups experienced similar reductions in the inflammatory markers IL-1, IL-10, and endotoxins. The length of hospital stay was also similar in both groups.

## #Dietitians

## Methionine metabolites and NAFLD 🗷

Elevated levels of methionine metabolites (S-adenosylhomocysteine and homocysteine) and a low Sadenosylmethionine/S-adenosylhomocysteine ratio were associated with a higher odds of nonalcoholic fatty liver disease and more severe hepatic steatosis in a Chinese cohort.

## Background

Methionine metabolites such as *S*-adenosylmethionine (S-Adenosyl Methionine), *S*-adenosylhomocysteine (SAH), and homocysteine (Hcy) are associated with cardiometabolic risk factors, but are they associated with nonalcoholic fatty liver disease (NAFLD)?

## The study

This cross-sectional study of 2,814 participants (ages 40–75) in China assessed the association between methionine metabolites and NAFLD. The investigators assessed serum methionine metabolites via fasting

blood samples and the presence of NAFLD via an abdominal ultrasound and a food frequency questionnaire (to exclude participants with alcoholic fatty liver disease). The authors graded the participants' severity of hepatic steatosis as "absent", "mild", "moderate", or "severe."

The authors also adjusted for the following confounders:

- Age
- Alkaline phosphatase (ALP, a liver enzyme)
- Aspartate aminotransferase/alanine aminotransferase ratio (AST/AST; ratio of two liver enzymes)
- BMI
- Drinking status
- Gender
- HDL-C
- High-sensitivity C-reactive protein
- LDL-C
- HOMA-IR
- Physical activity
- Smoking status
- Total cholesterol
- Triglycerides
- Trunk fat ratio
- Uric acid
- Waist-to-hip ratio
- History of hypertension, diabetes, dyslipidemia, and heart disease

#### The results

Overall, 1,446 participants (51.4%) had NAFLD. The odds of NAFLD increased with increasing SAH and Hcy levels, whereas there was no association between SAM and odds of NAFLD. In addition, serum SAH, HCY, and a low SAM/SAH ratio were correlated with the severity of hepatic steatosis.

## #Dietitians, #LiverDisease

## N-acetylcysteine for acute liver failure 🛛

This meta-analysis found that N-acetylcysteine improved transplant-free survival and reduced the length of hospital stay in patients with non-acetaminophen-induced acute liver failure.

## Background

Acute liver failure is a rare and life-threatening condition, which accounted for 3.3% of liver transplants in adults in 2017.<sup>[333]</sup> *N-acetylcysteine* (NAC) is often used for acetaminophen-induced acute liver failure. However, the evidence to date on NAC for *non-acetaminophen-induced acute liver failure* (NALF) is unclear.

## The study

This meta-analysis assessed whether NAC improved overall mortality for patients with NALF. As secondary outcomes, the authors assessed transplant-free survival, length of hospital stay, and occurrence of adverse events.

The inclusion criteria specified that studies be prospective, compare NAC to a control group, and have a length of follow-up between 3 weeks and 6 months. The authors excluded liver failure due to alcohol. They ultimately included 5 prospective studies assessing 672 total patients (334 receiving NAC and 338 as controls). The most common cause of NALF was viral hepatitis, followed by drug-induced liver injury, indeterminate cause, and autoimmune hepatitis.

Despite the inclusion criteria specifying that studies be prospective, 3 of the studies were randomized double-blinded trials that randomized patients to receive NAC or dextrose (a placebo) via IV. The other 2 studies compared outcomes from patients who received NAC via IV to retrospective data from patients who did not receive NAC.

## The results

Overall survival was not significantly improved with NAC, although there was a nonsignificant trend favoring NAC (70.1% survived in the NAC group vs. 59.8% in the control group). However, NAC improved transplant-free survival (51% vs. 28.1%) and reduced patient length of hospital stay. There were no differences between groups in the number of adverse events.

## #Dietitians

## 🥑 Low-Carb & Keto

## Comparing low- and high-carbohydrate diets for physical performance 🗷

This study had physically active people eat a high-carbohydrate diet for 3 weeks and then switch to a lowcarbohydrate diet for 3 weeks. Aerobic performance was better with the high-carbohydrate diet.

## Background

*High-carbohydrate* (HC) diets are frequently recommended for athletes, particularly during more sustained (e.g., >1 hour) aerobic activities.<sup>[135]</sup> However, there has been a growing body of research examining whether *low-carbohydrate* (LC) diets, by increasing the ability to metabolize fat for energy, can support physical performance to a similar degree. In general, studies have found reductions in exercise performance as a result of an LC diet,<sup>[136]</sup> but more research is needed.

## The study

This nonrandomized crossover trial examined the effects of an LC diet and an HC diet on physical performance and body composition among 18 physically active adults (mean age of 29, mean body mass index of 21.8).

The participants were assigned to an HC diet (75–80% of calories from carbohydrates, 15% from protein, and 5–10% from fat) for 3 weeks, followed by an LC diet (5–7% of calories from carbohydrates, 15% from protein, and 80% from fat) for 3 weeks, with a 3-week washout period between diets. For the HC diet, the focus was on eating complex carbohydrates (e.g., brown rice and potatoes) and avoiding sugar. For the LC diet, fish, meat, nuts, vegetables, and dairy products were the focus.

The outcomes examined included body composition, aerobic performance, and self-reported dietary intake. Aerobic performance was tested using a cycle ergometer, performed until exhaustion.

## The results

Compared with the LC diet, the HC diet resulted in higher peak aerobic performance (measured in watts, which represents the amount of power produced; HC: 251 watts, LC: 240 W) and a longer time to exhaustion (HC: 14.5 minutes, LC: 14.1 minutes).

Carbohydrate intake was higher (HC: 74%, LC: 7%) and kilocalorie (kcal) intake was lower (HC: 1,739 kcal, LC: 1,939 kcal) during the HC diet. On the LC diet, fat (HC: 68.5%, LC: 13.6%) and protein intake (HC: 13.6%, LC: 22.1%) were higher.

#### Note

One weakness with this study is its lack of randomization. Normally, crossover trials assign the order of

interventions to participants randomly. This study did not, instead assigning all participants to follow the HC diet first. This introduces the possibility of "order effects". For example, the participants could have performed worse on the aerobic test during the LC diet period because they had already done the test and found it boring.

## #SportsNutrition

## Low-carbohydrate diets for weight loss in people with obesity 🗷

Low-carbohydrate diets reduced body weight and BMI more than non-carbohydrate-restricted diets in participants with obesity, but the differences between the dietary approaches waned over time.

## Background

Although previous meta-analyses have confirmed the effectiveness of low-carbohydrate diets for weight loss, many of these meta-analyses included trials in people without obesity. Moreover, the results of some of the meta-analyses were driven largely by short-term trials, without separate analyses for longer-term trials. This meta-analysis aimed to overcome those limitations.

## The study

This meta-analysis of 25 randomized controlled trials (with a minimum duration of 12 weeks) examined the effects of low-carbohydrate diets, compared to non-carbohydrate-restricted diets, on body weight and BMI in participants with obesity.

The secondary outcomes were blood lipids and systolic blood pressure. All outcomes were assessed at 3–4, 6–8, 10–14, and 18–30 months.

The diets were defined as follows:

- Low-carbohydrate diets: <45% of total calories from carbohydrates or <130 grams of carbohydrates daily
- Non-carbohydrate-restricted diets: 45–60% of total calories from carbohydrates

## The results

Low-carbohydrate diets reduced body weight by around 2.6 kilograms more than non-carbohydraterestricted diets at 3–4 and 6–8 months. However, no differences between the dietary approaches were observed at 10–14 and 18–30 months. Similarly, low-carbohydrate diets reduced BMI by 1.7 more than non-carbohydrate-restricted diets at 3–4 months, but not at 6–8, 10–14, or 18–30 months.

For the secondary outcomes, compared to non-carbohydrate-restricted diets, low-carbohydrate diets improved HDL-C at 10–14 and 18–30 months and triglycerides at 3–4, 10–14, and 18–30 months.

The quality of the evidence was high for body weight at 3-4, 6–8, and 10–14 months and BMI at 3-4

months; moderate for body weight at 18-30 months and BMI at 6–8 and 10–14 months; and low for BMI at 18–30 months.

#Dietitians

## **O Men's Health & Testosterone**

## Bisphenol A and semen quality – how much BPA is safe for men?

This systematic review determined a tolerable daily intake for bisphenol A (3 nanograms per kilogram of body weight) that can be safely consumed to avoid declines in semen quality. To reach this level of bisphenol A exposure, the average man would have to consume about 100 canned beverages per day.

#### Background

*Bisphenol A* (BPA) is a component of plastic and epoxy manufacturing and is found in the lining of many consumer products, such as cans. Because BPA is also an estrogen analogue, it may cause a variety of health problems. For instance, BPA is thought to interfere with men's reproductive health — a claim based on animal<sup>[179]</sup> and observational evidence.<sup>[180]</sup>

However, it's not yet clear how much BPA can be safely consumed before health problems start to occur. This study aimed to define a *tolerable daily intake* (TDI) level of BPA that can be safely consumed without interfering with men's reproductive health.

#### The study

This systematic review of 26 animal and 16 cohort studies investigated the association between BPA exposure and declines in semen quality as part of a risk assessment to determine a TDI for BPA. The researchers focused on the effects of gestational BPA exposure (i.e., BPA exposure during pregnancy) in animal studies.

## The results

The researchers found convincing evidence of lower semen quality after gestational BPA exposure in animal studies. This finding was supported by human cohort studies showing an association between BPA exposure and declines in semen quality.

Based on their systematic analysis, the researchers proposed a TDI of 3 nanograms of BPA per kilogram of body weight (ng/kg), which corresponds to a TDI of 500–600 ng of BPA for the average person.

#### Note

The estimated TDI values for BPA vary widely in the literature. Although the EFSA proposed 4,000 ng/kg in 2015, they revised their estimate to 0.04 ng/kg in 2021 – a reduction of 100,000 times! Also, BPA intake can vary widely depending on the type of canned products consumed, making it difficult to determine one's personal BPA exposure.

## #Dietitians

## 💋 Muscle Gain & Exercise

## Do genetics modulate caffeine's performance-enhancing effects?

Participants with the gene encoding for "fast" caffeine metabolism demonstrated a greater effect of caffeine on peak power output than those with the gene encoding for "slow" or "ultraslow" caffeine metabolism.

## Background

Caffeine has ergogenic (performance-enhancing) effects at doses of 3–6 milligrams per kilogram of body mass (mg/kg) when taken approximately 60 minutes before exercise. However, there is considerable variability between individuals in its effects, partly due to genetics.

The CYP1A2 gene determines the rate of caffeine metabolism — people with an AA genotype are "fast" metabolizers, whereas those with AC and CC genotypes are "slow" and "ultraslow" caffeine metabolizers, respectively. Can CYP1A2 genotype modulate caffeine's ergogenic effects?

## The study

This crossover randomized controlled trial assessed the effects of CYP1A2 polymorphism on caffeine's ergogenic potential. Sixteen men (average age of 22), with at least one year of resistance training experience and a low habitual caffeine intake (<100 mg/day) were randomized to supplement with 6 mg/ kg of caffeine or a placebo approximately 60 minutes before an all-out 30-second cycling test. The placebo and caffeine conditions were separated by 7 days, and both the participants and investigators were blinded to the treatment condition.

The authors assessed fatigue index and peak, average, and minimum power outputs during the cycling tests. The participants provided blood samples for assessment of CYP1A2 genotype — 10 participants had AA, 5 had AC, and 1 had CC (the authors grouped the AC and CC participants together in their analysis).

## The results

The participants with the AA genotype improved their peak power output following caffeine, compared to placebo, but the participants with the AC/CC genotypes did not. However, there were no differences between genotypes in caffeine's effect on average power output, minimum power output, or fatigue index.

## Note

Although individuals with the AA genotype might experience a greater ergogenic effect following caffeine supplementation than those with AC or CC genotypes, the evidence is mixed. A recent systematic review of 14 studies reported differences between genotypes in only 4 studies, all of which favored the AA genotype.<sup>[116]</sup>

As previously reviewed in *Study Summaries*, the CYP1A2 genotype can affect more than just performance outcomes. Some evidence suggests that higher caffeine intakes increase the risk of insulin resistance,<sup>[117]</sup> heart attacks,<sup>[118]</sup>, and high blood pressure<sup>[119][120]</sup> in intermediate and slow but not rapid caffeine metabolizers.<sup>[121]</sup>

#### #Dietitians, #SportsNutrition

## Can creatine improve sprinting performance?

This randomized-controlled trial found that creatine had a small but notable effect on repeated sprinting performance. During the last 5 seconds of the last sprint, creatine improved speed and power output by a few percent compared to placebo.

#### Background

Creatine supplementation reduces fatigue during repeated high-intensity exercise.<sup>[204]</sup> However, most studies tested durations of 30 seconds, which are not common in sports, and used cycling instead of running-based sprint tests. This study examined whether creatine can improve repeated sprinting exercises during shorter sprint periods.

#### The study

This randomized controlled trial in 16 healthy, physically active men (average age of 26) examined whether oral creatine supplementation can improve sports performance during repeated sprint tests compared to a placebo. At baseline, all participants received placebo supplementation for 5 days and then performed repeated sprint tests (six repetitions of 10 seconds each on a nonmotorized treadmill). Afterward, the subjects received either a placebo or creatine (75 milligrams per kilogram of body weight daily) for 5 days and repeated the sprint test protocol.

During the six sprints, the researchers measured the mean and maximum power output and running speed. They also measured maximal oxygen uptake (VO<sub>2</sub>max) to assess the possible effects of creatine on aerobic metabolism.

#### The results

Creatine slightly improved mean speed and power output in the last 5 seconds of the last sprint by a few percent. This effect was not observed in the placebo group. Otherwise, no differences between creatine and placebo were found for sprinting performance. Also, no differences in VO<sub>2</sub>max were found, indicating that creatine had no effect on aerobic performance.

#### Note

The creatine group experienced a small but notable increase in body mass index, which was not observed in the placebo group. Because the researchers did not measure body composition, it remains unclear whether the weight gain was due to water retention or muscle gain. If creatine led to improved recovery
after the first sprinting test, the results could equally be explained by the muscle gain, not the creatine itself. Future studies should account for changes in body composition when testing the effects of creatine on exercise performance.

## #SportsNutrition

## The effect of maltodextrin-based mouth rinsing on exercise performance 🗷

*This meta-analysis of 34 randomized controlled trials reported that maltodextrin-based mouth rinses may improve exercise performance.* 

## Background

A robust body of evidence demonstrates that ingesting carbohydrates during endurance exercise enhances performance, <sup>[256]</sup> but it can also cause gastrointestinal discomfort, which may negatively affect performance. A potential alternative is a carbohydrate mouth rinse, but the evidence is mixed on whether they enhance exercise performance. These differences may stem from the type of exercise and the rinsing protocol.

## The study

This meta-analysis of 34 randomized controlled trials examined the effect of a maltodextrin-based oral rinse on exercise performance in 444 participants (380 men and 64 women). The duration of rinsing ranged from 5 to 40 seconds, but the majority of participants rinsed for 5–10 seconds. Also, the carbohydrate concentration of the rinse ranged from 5 to 12%, but most studies used 6.4%. The most common exercise protocol was a cycling time trial, followed by resistance training, and sprinting. Other exercise protocols included a time-to-exhaustion cycling test and running test, a running time trial, and isometric contractions. Subgroup analyses were performed based on the concentration of the mouth rinse, the duration of mouth rinsing, the exercise protocol, and whether the participants fasted before using the mouth rinse.

## The results

There was a small increase in exercise performance with maltodextrin-based mouth rinses compared with the placebo. According to the subgroup analyses, rinsing for 10 seconds was most effective, and a carbohydrate concentration of 6–6.5% was more effective than 8–18%.

#### Note

Due to the wide variability in the mouth rinse and exercise protocol between studies, the results should be interpreted with caution.

## #SportsNutrition

## The effect of vitamin C and E supplementation on recovery from exercise

This meta-analysis found that a combination of vitamins C and E reduced some markers of oxidative stress and inflammation immediately after exercise but not 24–96 hours after exercise. Supplementation also reduced creatine kinase levels at 48 hours after exercise.

## Background

High-intensity exercise transiently increases oxidative stress, inflammation, and muscle damage, which manifests as delayed onset muscle soreness, reduced functionality, and impaired physical performance.<sup>[260][261]</sup> Vitamins C and E have antioxidant properties, so they have the potential to mediate levels of oxidative stress and inflammation after exercise and reduce adverse effects, like excessive delayed onset muscle soreness, that often deter people from sticking to an exercise program.

## The study

This meta-analysis of 18 randomized controlled trials (published between 1994 and 2019) investigated the effect of combined supplementation with vitamins C and E on oxidative stress, inflammatory markers, muscle damage, muscle soreness, and muscle strength in 322 participants. The dose of vitamin C ranged from 200 to 2,000 milligrams (mg), and the dose of vitamin E ranged from 259 to 1,400 IU for a period of 14–42 days before the exercise protocol. The majority of studies (58%) used an aerobic exercise protocol.

The outcomes were assessed immediately postexercise and up to 96 hours postexercise. Markers of oxidative stress included malondialdehyde, thiobarbituric acid reactive substances, F2-isoprostanes, and hydrogen peroxides. Markers of inflammation included *interleukin* (IL)-1Ra, IL-6, and C-reactive protein. Markers of muscle damage included creatine kinase and lactate dehydrogenase.

## The results

Immediately after exercise, there was a moderate reduction in oxidative stress and IL-6 and a large reduction in cortisol with vitamin supplementation compared to placebo. Additionally, there was a large reduction in creatine kinase levels at 48 hours postexercise with vitamin supplementation compared to placebo.

## Note

The studies included mostly men, so some caution is needed in extending these findings to women. Additionally, the findings were largely based on "very low" quality of evidence. Another limitation is that subgroup analyses were not performed to determine whether the effects of vitamin C and E supplementation differed based on the type of exercise performed (i.e., aerobic versus anaerobic exercise), the dose and duration of supplementation, and the training status of the participants (i.e., athletes versus untrained individuals).

Although vitamin C and E supplementation may improve recovery from exercise, it may also blunt the physiological adaptations evoked by exercise. Therefore, the best time to consider vitamin C and E supplementation is when recovery and peak performance are more important (e.g., during the

competitive season) than physiological adaptations (e.g., during the off-season).

## #SportsNutrition

## Does probiotic supplementation improve aerobic exercise performance?

This meta-analysis of 12 randomized controlled trials found that probiotic supplementation had a small positive effect on aerobic exercise performance.

## Background

Probiotics are live microorganisms that confer health benefits when administered in adequate amounts. The most common strains belong to the *Bifidobacterium* or *Lactobacillus* genera. Probiotic supplementation may improve aerobic exercise performance by enhancing intestinal barrier function and preventing gastrointestinal side effects during exercise or by increasing carbohydrate metabolism.<sup>[284][285]</sup> However, the evidence is mixed on whether probiotic supplementation improves aerobic exercise performance.

#### The study

This meta-analysis of 12 randomized controlled trials investigated the effect of probiotic supplementation on aerobic-metabolism-predominant exercise (i.e., continuous exercise that lasted  $\geq$  5 minutes) in 232 trained participants (i.e., people who performed  $\geq$  8 hours of exercise or  $\geq$  5 workouts per week). Seven studies used a single-strain probiotic, and 5 studies used a multistrain probiotic. The intervention duration varied from 3 weeks to 14 weeks. The time of supplementation also varied between studies. For example, two studies had the participants ingest the supplement after the first meal of the day, 2 studies had the participants ingest the supplement during any meal, and 2 studies had the participants ingest the supplement after exercise and before sleeping.

#### The results

There was a small improvement in aerobic exercise performance with probiotic supplementation. Greater effects were reported with higher supplementation doses, single-strain probiotics, time-to-exhaustion tests (as opposed to VO<sub>2</sub>max tests), and in studies  $\leq$  4 weeks long. The duration of exercise didn't meaningfully influence the effect of probiotic supplementation.

#### Note

The effects of probiotics are strain specific, and a wide variety of strains were included in this study. Therefore, although some single-strain probiotic supplements may improve aerobic exercise performance, it's unclear which strain is the most effective.

## #SportsNutrition

## Can chronic L-arginine supplementation improve exercise performance?

This crossover trial compared the effects of short-term and long-term L-arginine supplementation on exercise performance. In both cases, L-arginine had no effects.

## Background

Although arginine is marketed for athletic performance, acute (short-term) supplementation in healthy adults has unreliable effects on *nitric oxide* (NO) production<sup>[304][305][306]</sup> and athletic performance.<sup>[307]</sup>

Chronic (long-term) supplementation with L-arginine could be more effective, but previous studies have showed inconsistent results.<sup>[308][309][310][311]</sup> One possible explanation is that the studies used different doses and durations of L-arginine supplementation. However, a direct comparison of the acute and chronic effects of L-arginine supplementation was needed.

## The study

This randomized controlled crossover trial in 16 healthy young men (average age of 23) compared the effects of acute and chronic L-arginine supplementation on sports performance.

In the acute trials, the participants took either 5 grams of L-arginine or a placebo prior to a cycling performance test. In the chronic trials, the participants took L-arginine (5 grams daily) for 2 weeks and then performed the same cycling performance test as in the acute group. The acute and chronic phases were separated by a washout period of 2 weeks.

To test whether L-arginine could attenuate the exercise-induced increase in ammonia, the researchers measured plasma ammonia concentrations at baseline and after the sports performance test.

## The results

Acute and chronic L-arginine supplementation had no effects on blood ammonia levels or exercise performance.

#### Note

This study was funded by a Japanese supplement company.

## #SportsNutrition, #ConflictofInterest

## Can cold or heat therapy reduce muscle soreness? 🛛

Of the cold and warm therapies assessed in this network analysis, heat pack therapy was most effective at reducing muscle soreness 24 and 48 hours after exercise. Cryotherapy was most effective at reducing muscle soreness >48 hours after exercise.

## Background

*Delayed onset muscle soreness* (DOMS) is muscle soreness in the hours or days following physical activity and can negatively affect exercise adherence and subsequent performance. Although many people use

cold-based or heat-based therapies after exercise to prevent DOMS, the effectiveness of these interventions is unclear.

## The study

This network analysis of randomized controlled trials compared the effectiveness of cold and heat therapies for DOMS.

Fifty-nine studies assessing 1,367 patients were included. The inclusion criteria specified that the participants received cold or heat therapy within 1 hour after exercise, and studies that repeated the intervention on subsequent days were included. Studies that used multiple recovery modalities in addition to cold or heat therapies were excluded. DOMS was assessed at baseline (preexercise) and at 24, 48, and >48 hours postexercise.

The following 10 interventions were examined:

- Contrast water therapy
- Phase change material
- Cryotherapy
- Cold water immersion
- Hot/warm water immersion
- Cold pack therapy
- Hot pack therapy
- Ice massage
- Ultrasound
- Passive recovery (a control condition)

## The results

Hot pack therapy was the most effective treatment for reducing DOMS at 24 hours after exercise, followed by contrast water therapy, followed by cryotherapy. Hot pack therapy was also the most effective at reducing DOMS at 48 hours, followed by cryotherapy, followed by phase change materials. Cryotherapy was the most effective at reducing DOMS >48 hours after exercise, followed by phase change materials, followed by contrast water therapy.

The authors reported evidence for possible publication bias.

## Note

Heat pack therapy involves applying heat wraps to a target muscle for several hours after exercise and

may reduce DOMS via increased blood flow and enhanced calcium influx through voltage-gated calcium channels.<sup>[338]</sup>

Contrast water therapy involves alternating between cold and warm water immersion. It may facilitate recovery via alternating between vasoconstriction and vasodilation, enhancement of blood flow, reductions in inflammation, or improved range of motion.<sup>[339]</sup>

Cryotherapy involves short exposure to extremely cold air and may reduce tissue swelling and inflammation.<sup>[340]</sup>

Phase change materials are clothing materials that absorb heat energy, resulting in a cooling effect, and may reduce DOMS via similar mechanisms as cryotherapy.<sup>[341]</sup>

#SportsNutrition

## Pain, Joints & Bones

## Undenatured type II collagen for improving knee joint flexibility 🗷

Supplementation with undenatured type II collagen made from chicken sternum cartilage improved knee joint flexibility in participants with activity-related knee joint discomfort.

## Background

Individuals with activity-related knee joint discomfort may have impaired knee joint flexibility. Because *undenatured type II collagen* (UC-II<sup>®</sup>; a patented type of undenatured collagen made from chicken sternum cartilage) has previously been reported to improve knee mobility both in individuals with osteoarthritis and in healthy individuals,<sup>[224][225]</sup> it may improve knee joint flexibility in people with activity-related knee joint discomfort.

## The study

In this 24-week randomized controlled trial, 96 healthy men and women (ages 20–55), who reported kneejoint discomfort during or immediately after physical activity and while performing a standardized singleleg step-down test, took capsules containing either 40 milligrams of UC-II<sup>®</sup> (providing ≥3% undenatured type II collagen) or a placebo.

The outcomes were knee flexion and knee extension *range of motion* (ROM) measured with a digital goniometer. Knee flexion ROM was measured every 4 weeks (i.e., at baseline and weeks 4, 8, 12, 16, 20, and 24), and knee extension was measured every 12 weeks (i.e., at baseline and weeks 12 and 24).

## The results

At the end of the study, knee flexion ROM improved more with UC-II<sup>®</sup> (+3.2°) compared with the placebo (+0.2°). The differences between groups were statistically significant from week 8 onwards. Knee extension ROM improved with UC-II<sup>®</sup> (+2.2°) but not with the placebo (+1.3°; statistically nonsignificant). However, a statistically significant difference between groups was not detected.

## #Dietitians

# 📶 Skin, Hair & Aesthetics

## The effects of dairy and glycemic content on acne 🗷

This systematic review found convincing evidence that a low glycemic diet can reduce acne. However, for dairy, the evidence was less clear; dairy was associated with acne only in Western populations, but not in other ethnic groups.

#### Background

The associations between acne and specific foods (such as dairy and sweets) have proven controversial,<sup>[87][88][89]</sup> mostly because studies involving diet are difficult to conduct. However, new evidence investigating the association between specific dietary factors and acne has been accumulating in recent years. Hence, a systematic review was warranted.

#### The study

This systematic review of 28 observational and 6 interventional studies examined the association between dairy and glycemic content and acne development. The researchers defined glycemic content in terms of glycemic index, glycemic load, and overall carbohydrate intake. They also investigated whether sex, ethnicity, and cultural dietary habits play a role in the relationship between diet and acne.

#### The results

There was a clear association between glycemic content and acne development, which was independent of sex, ethnicity, and cultural habits. This association was also backed up by 6 interventional studies showing improvements in acne when participants switched to a diet low in glycemic content.

For dairy, however, the results were mixed, and only observational (but not interventional) studies were available. Dairy intake was associated with acne in Western populations, but not in other ethnic groups.

#### Note

Because most identified studies focused on young men and women in their teens and twenties, the results of this study are limited to this age group. Also, most of the participants in observational studies were women, whereas most subjects in interventional studies were men. This is problematic, given the known differences in hormones and sex-specific effects of diet on acne.

#### **#Dietitians**

## 🕮 Vegan & Vegetarian

## Cardiometabolic health in omnivores and vegetarians 🗷

This cross-sectional study found that vegetarians may exhibit better arterial stiffness (especially in men) and some better cardiometabolic biomarkers than omnivores, but diet quality and its association with health outcomes depends on many other complex variables.

## Background

Arterial stiffness is an indicator of vascular aging and risk of hypertension and is a strong predictor of cardiovascular mortality.<sup>[125]</sup> Dietary patterns that emphasize whole plant foods, such as the DASH or Mediterranean diet, are inversely associated with arterial stiffness and cardiometabolic health biomarkers.<sup>[126]</sup> Do omnivores and vegetarians differ in arterial stiffness and other cardiometabolic health biomarkers?

## The study

This cross-sectional study involved 42 healthy participants (average age of 35 years old; 21% male), of which 22 were omnivores and 20 were vegetarians (by self-report).

Arterial stiffness, blood pressure, fasting cardiometabolic and inflammatory biomarkers (lipoproteins and high-sensitivity C-reactive protein), and anthropometrics (body measurements) were measured. For analysis, omnivores were matched with vegetarians based on BMI.

## The results

Arterial stiffness, blood pressure, and cardiometabolic health biomarkers did not differ between omnivores and vegetarians, except that omnivores had higher HDL-C levels. Arterial stiffness and triglyceride/HDL-C ratio (a predictor of coronary disease risk)<sup>[127]</sup> suggested a decrease for vegetarians, but this difference did not reach statistical significance.

In a subgroup analysis based on sex, male vegetarians had lower arterial stiffness than male omnivores. Omnivores had a higher BMI and hip circumference than vegetarians.

#### Note

These results should be interpreted with caution because eating patterns were based on self-reports and were not verified by any means (e.g., dietary assessment), the sample was rather small (especially for subgroup analyses), and dietary nutrient intake was not monitored. There is much more nuance to the associations between dietary patterns and health outcomes than this study was able to address.

Plant-based diets are often promoted for healthier outcomes, but this dietary distinction can still include

highly processed, less healthy foods and an overall lower-quality diet that is associated with poorer health outcomes. To properly guide consumers toward a diet that promotes healthier outcomes, attention should be focused on the healthy aspects of plant-based diets, such as richness in fiber, micronutrients, and phytochemicals that come mostly from whole foods.<sup>[128]</sup>

## #Dietitians

## Do low-protein vegetarian diets improve renal function in chronic kidney disease? 🗷

This scoping review found no convincing evidence that a low-protein vegetarian diet improves renal function more effectively than a conventional low-protein diet in the context of chronic kidney disease.

## Background

Protein restriction is recommended for patients with *chronic kidney disease* (CKD) to sustain renal function and reduce the risk of renal failure.<sup>[245]</sup> Additionally, the source of dietary protein may be relevant for CKD management. For instance, vegetarian diets (no fish or meat) could have beneficial effects in maintenance of renal function<sup>[246]</sup> (e.g., by reducing uremic toxins.<sup>[247]</sup>) However, the risks and benefits of a vegetarian diet for CKD treatment remain unclear.

## The study

This scoping review of 4 studies — 2 crossover, 1 cross-sectional, and 1 *randomized controlled trial* (RCT) — examined the effects of a vegetarian diet on renal function in 324 adults with CKD who were not on dialysis.

The RCT was the study with the most participants (207 adults) and the one conducted for the longest time (15 months). In the RCT, a low-protein (0.3 grams of protein per kilogram of body weight or 0.3 g/kg) vegetarian diet supplemented with essential amino acids was compared to a conventional low-protein diet (0.6 g/kg).<sup>[248]</sup>

## The results

Of the 4 studies, only the RCT showed beneficial effects of a low-protein vegetarian diet (supplemented with ketoanalogues) compared to a conventional low-protein diet. The RCT found that only 11% in the vegetarian group reached renal failure compared to 30% in the control group.<sup>[248]</sup>

## Note

Because protein content and amino acid supplementation differed between the control and treatment group, the results of the RCT cannot be attributed only to the vegetarian diet or type of protein source.

## #Dietitians, #ChronicKidneyDisease

## The vegan metabolome: Is it different? And does different mean better? 🛛

In this cross-sectional study, vegans showed marked differences in metabolite profiles compared to omnivores. In most cases, metabolite concentrations were lower in vegans than omnivores, including certain disease risk factors.

## Background

Vegan diets are associated with many positive health outcomes, such as a lower risk of diabetes<sup>[287][288]</sup> and cardiovascular disease.<sup>[289][290]</sup> However, the biological mechanisms behind these health benefits remain elusive. It's possible that a vegan diet may positively influence the metabolome, which is the complete set and interactions of metabolites (small molecules produced during metabolic processes) in the body. For example, vegans may have lower levels of lipid metabolites.<sup>[291]</sup> This study explored whether eating a vegan diet changes the abundance of plasma metabolites compared to an omnivorous diet.

## The study

This cross-sectional study examined whether eating a plant-based diet influences plasma metabolic profiles compared to an omnivorous diet (defined as consuming at least 28 grams of red meat per day). The 96 healthy adult (average of 61) participants were part of the Adventist Health Study-2 cohort, a large cohort established in 2002–2007 that is well suited to studying the relationship between plant-based dietary patterns and health and disease risk.

To identify plasma metabolites in participant blood samples, the researchers used liquid chromatography (a method that physically separates molecules in complex solutions) coupled with mass spectrometry (an analytical instrument that detects the presence and concentration of hundreds of metabolites).

## The results

The researchers identified 930 metabolites and 93 metabolite subclasses such as lipids, amino acids, carbohydrates, nucleotides (building blocks of DNA), and xenobiotics (chemical substances foreign to animal cells such as drugs or pesticides).

Of the 930 analyzed metabolites, 586 (63%) showed a different abundance in vegans than in omnivores. Of these 586 differential metabolites, 164 (28%) were higher and 422 (72%) were lower in vegans. The metabolites showing the greatest changes were lipids, amino acids, and xenobiotics.

Of the 93 metabolite subclasses, 50 subclasses were changed in vegans relative to omnivores. Most notably, vegans had higher ketone, vitamin A, and inositol metabolism and lower drug, xanthine, and fatty acid metabolism.

The researchers noted that many of these metabolites and metabolite subclasses may be involved in inflammation, insulin dysregulation, and cardiometabolic phenotypes (the observable characteristics of an organism). However, the causal effects of these metabolite changes on health outcomes remain unknown.

## Note

There are two limitations worth mentioning. First, the vegans differed from the omnivores in many ways other than diet. Most notably, the vegans had a lower BMI, a lower intake of calories and saturated fats, and a higher consumption of fruits, vegetables, whole grains, and dietary fiber than the omnivores. As such, these confounders could have influenced the results.

Second, the results of this cross-sectional study cannot infer a causal relationship between certain metabolite changes and health outcomes. In other words, it remains unclear whether the observed metabolite changes directly lead to improved health outcomes. Larger and longer cohort studies are needed to further investigate this hypothesis.

#### **#Dietitians**

## What's in your cheese alternative? 🛛

This cross-sectional study assessed the nutritional content of nondairy plant-based cheese alternatives available in the United States. Very few products were fortified with calcium, vitamin D, and/or vitamin B<sub>12</sub>, and most were poor sources of protein.

## Background

Nondairy plant-based cheeses have been increasing in popularity due to concerns related to health (e.g., lactose intolerance), the environment, and animal welfare.

Dairy cheese is considered a decent source of protein and calcium. When people choose a nondairy plantbased cheese alternative, they often expect a product with not only similar taste and texture, but also similar nutritional content. How does nondairy plant-based cheese stack up against dairy cheese in terms of nutritional content?

## The study

This cross-sectional study evaluated the nutritional content of 245 nondairy plant-based cheese alternatives (representing 35 brands) available in the United States using either the nutritional facts label on the retail package or data collected from the manufacturer's website.

The cheese alternatives were based on coconut oil (106 products), cashews and coconut oil (61 products), cashews (35 products), oats (16 products), almonds (7 products), soy (6 products), palm fruit oil (5 products), and other blends (9 products). The nutritional value of the products was determined by whether they were fortified with calcium, vitamin D, and/or vitamin B<sub>12</sub>, as well as the amount of calories, total fat, saturated fat, protein, and sodium that they provided per serving.

## The results

Overall, cashew-based products tended to provide the most protein and the least amount of sodium per

serving, while coconut-based products tended to provide the most saturated fat and sodium per serving.

Of the 245 products:

- Only 19 (7.8%) were fortified with calcium, 1 (0.4%) was fortified with vitamin D, and 14 (5.7%) were fortified with vitamin B<sub>12</sub>.
- Only 3 products (1.2%) provided at least 5 grams of protein per serving, and 183 (75%) provided ≤ 2.5 grams of protein per serving.
- 15 products (6.1%) provided ≤ 115 milligrams (mg) of sodium per serving, while 31 (13.1%) provided ≥ 230 mg of sodium per serving.
- 14 products (5.7%) provided ≤ 1 gram of saturated fat per serving, while 57 (23.3%) provided ≥ 4 grams of saturated fat per serving.
- 4 products (1.6%) provided ≤ 4 grams of total fat per serving, and 81 (33.1%) provided ≤ 100 calories per serving.

#### Note

Because this study only analyzed products available in the United States, the results may not apply to the nutritional content of nondairy plant-based cheese alternatives in other countries.

## #Dietitians

## Do vegetarians have better cardiovascular health than nonvegetarians?

In this cross-sectional study, vegetarians had better cardiovascular health metrics than omnivores (with the exception of diet). In contrast, diet scores were lower in vegetarians, probably due to their lack of fish consumption.

## Background

Vegetarian diets have potentially beneficial effects on *cardiovascular* (CV) health.<sup>[330]</sup> However, most studies did not account for metabolic profiles and lifestyle habits such as diet, smoking, and physical activity. This study asked whether vegetarian diets are associated with CV health while also taking into account metabolic profiles and lifestyle habits.

## The study

This cross-sectional study in 1,896 healthy Taiwanese adults (ages 46–66) investigated whether a vegetarian diet (i.e., eating no meat or fish) is associated with better CV health.

The researchers used the ideal CV health metric to measure CV health via seven CV risk factors: diet, smoking, blood pressure, physical activity, fasting glucose, total cholesterol, and BMI.<sup>[331]</sup> The results were adjusted for age, gender, education level, and family income.

## The results

Overall, vegetarians had better CV health than omnivores with respect to five risk factors: smoking, blood pressure, fasting glucose, total cholesterol, and BMI. However, vegetarians had a lower healthy diet score than omnivores, probably due to a lack of fish consumption. Physical activity was similar between both groups. These results remained consistent after adjusting for confounding factors.

#### Note

Because fish was one of the components of the healthy diet score, it is not surprising that the vegetarians in this study (defined as not eating fish or meat) had a lower score than omnivores. Future studies using the ideal CV health metric might need to modify the score for vegetarians (e.g., by replacing fish with other omega-3 fatty acid sources such as walnuts or flaxseeds).

#### **#Dietitians**

## Bibliography

- 1. Jing Chun Ng, Yik Weng Yew Effect of Vitamin D Serum Levels and Supplementation on Atopic Dermatitis: A Systematic Review and Meta-analysis. *Am J Clin Dermatol.* (2022 Mar 5)
- Nina Ramessar, Abhilasha Borad, Naomi Schlesinger The effect of Omega-3 fatty acid supplementation in systemic lupus erythematosus patients: A systematic review. *Lupus*. (2022 Mar)
- 3. Howard D Sesso, Pamela M Rist, Aaron K Aragaki, Susanne Rautiainen, Lisa G Johnson, Georgina Friedenberg, Trisha Copeland, Allison Clar, Samia Mora, M Vinayaga Moorthy, Ara Sarkissian, Jean Wactawski-Wende, Lesley F Tinker, William R Carrick, Garnet L Anderson, JoAnn E Manson, COSMOS Research Group Multivitamins in the prevention of cancer and cardiovascular disease: The COSMOS randomized clinical trial. *Am J Clin Nutr*. (2022 Mar 16)
- 4. Charlotte Debras, Eloi Chazelas, Bernard Srour, Nathalie Druesne-Pecollo, Younes Esseddik, Fabien Szabo de Edelenyi, Cédric Agaësse, Alexandre De Sa, Rebecca Lutchia, Stéphane Gigandet, Inge Huybrechts, Chantal Julia, Emmanuelle Kesse-Guyot, Benjamin Allès, Valentina A Andreeva, Pilar Galan, Serge Hercberg, Mélanie Deschasaux-Tanguy, Mathilde Touvier Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. *PLoS Med*. (2022 Mar 24)
- 5. Kaitlyn L I Samson, Jordie A J Fischer, Marion L Roche Iron Status, Anemia, and Iron Interventions and Their Associations with Cognitive and Academic Performance in Adolescents: A Systematic Review. *Nutrients*. (2022 Jan 5)
- Kazumasa Yamagishi, Koutatsu Maruyama, Ai Ikeda, Masanori Nagao, Hiroyuki Noda, Mitsumasa Umesawa, Mina Hayama-Terada, Isao Muraki, Chika Okada, Mari Tanaka, Rie Kishida, Tomomi Kihara, Tetsuya Ohira, Hironori Imano, Eric J Brunner, Tomoko Sankai, Takeo Okada, Takeshi Tanigawa, Akihiko Kitamura, Masahiko Kiyama, Hiroyasu Iso Dietary fiber intake and risk of incident disabling dementia: the Circulatory Risk in Communities Study. Nutr Neurosci. (2022 Feb 6)
- 7. Joaquín García-Cordero, Alicia Pino, Constanza Cuevas, Verónica Puertas-Martín, Ricardo San Román, Sonia de Pascual-Teresa Neurocognitive Effects of Cocoa and Red-Berries Consumption in Healthy Adults. *Nutrients*. (2021 Dec 21)
- 8. Patricia L East, Brie Reid, Estela Blanco, Raquel Burrows, Betsy Lozoff, Sheila Gahagan Iron supplementation given to nonanemic infants: neurocognitive functioning at 16 years. *Nutr Neurosci*. (2021 Dec 19)
- 9. Mathieu Maltais, Dominique Lorrain, Pauline Léveillé, Isabelle Viens, Annick Vachon, Anita Houeto, Nancy Presse, Mélanie Plourde Long-chain Omega-3 fatty acids supplementation and cognitive

performance throughout adulthood: A 6-month randomized controlled trial. *Prostaglandins Leukot Essent Fatty Acids*. (2022 Mar)

- 10. Néma D McGlynn, Tauseef Ahmad Khan, Lily Wang, Roselyn Zhang, Laura Chiavaroli, Fei Au-Yeung, Jennifer J Lee, Jarvis C Noronha, Elena M Comelli, Sonia Blanco Mejia, Amna Ahmed, Vasanti S Malik, James O Hill, Lawrence A Leiter, Arnav Agarwal, Per B Jeppesen, Dario Rahelic, Hana Kahleová, Jordi Salas-Salvadó, Cyril W C Kendall, John L Sievenpiper Association of Low- and No-Calorie Sweetened Beverages as a Replacement for Sugar-Sweetened Beverages With Body Weight and Cardiometabolic Risk: A Systematic Review and Meta-analysis. JAMA Netw Open. (2022 Mar 1)
- 11. Yoonhye Kim, Yun Kyoung Oh, Junhee Lee, Eunyoung Kim Could nutrient supplements provide additional glycemic control in diabetes management? A systematic review and meta-analysis of randomized controlled trials of as an add-on nutritional supplementation therapy. *Arch Pharm Res.* (2022 Mar)
- 12. Baolan Ma, Jialin Lu, Tong Kang, Ming Zhu, Ke Xiong, Jinyu Wang Astaxanthin supplementation mildly reduced oxidative stress and inflammation biomarkers: a systematic review and metaanalysis of randomized controlled trials. *Nutr Res.* (2022 Mar)
- Kevin D Hall, I Sadaf Farooqi, Jeffery M Friedman, Samuel Klein, Ruth J F Loos, David J Mangelsdorf, Stephen O'Rahilly, Eric Ravussin, Leanne M Redman, Donna H Ryan, John R Speakman, Deirdre K Tobias The energy balance model of obesity: beyond calories in, calories out. Am J Clin Nutr. (2022 Feb 4)
- 14. Petek Eylul Taneri, Faina Wehrli, Zayne M Roa Diaz, Oche Adam Itodo, Dante Salvador, Hamidreza Raeisi-Dehkordi, Lia Bally, Beatrice Minder, Jessica C Kiefte-de Jong, Jessica Laine Carmelli, Arjola Bano, Marija Glisic, Taulant Muka Association Between Ultra-Processed Food İntake and All-Cause Mortality: A Systematic Review and Meta-Analysis. Am J Epidemiol. (2022 Mar 1)
- Maximilian Andreas Storz, Gianluca Rizzo, Alexander Müller, Mauro Lombardo Bowel Health in U.S. Vegetarians: A 4-Year Data Report from the National Health and Nutrition Examination Survey (NHANES). Nutrients. (2022 Feb 6)
- Ce Sun, Wei-Sen Zhang, Chao-Qiang Jiang, Ya-Li Jin, Xue-Qing Deng, Jean Woo, Kar-Keung Cheng, Tai-Hing Lam, G Neil Thomas, Lin Xu Low-Carbohydrate Diets and Mortality in Older Asian People: A 15-Year Follow-Up from a Prospective Cohort Study. Nutrients. (2022 Mar 28)
- 17. Abrar Alhebshi, Nehal Alsharif, Josh Thorley, Lewis J James, Tom Clifford The Effects of Dietary Protein Supplementation on Exercise-Induced Inflammation and Oxidative Stress: A Systematic Review of Human Trials. *Antioxidants (Basel)*. (2021 Dec 22)
- 18. Elena S George, Anjana Reddy, Amanda J Nicoll, Marno C Ryan, Catherine Itsiopoulos, Gavin Abbott, Nathan A Johnson, Siddharth Sood, Stuart K Roberts, Audrey C Tierney Impact of a

Mediterranean diet on hepatic and metabolic outcomes in non-alcoholic fatty liver disease: The MEDINA randomised controlled trial. *Liver Int*. (2022 Mar 31)

- 19. Robert Ross, Amy E Latimer-Cheung, Andrew G Day, Andrea M Brennan, James O Hill A small change approach to prevent long-term weight gain in adults with overweight and obesity: a randomized controlled trial. *CMAJ*. (2022 Mar 7)
- 20. Sandeep Dhindsa, Husam Ghanim, Todd Jenkins, Thomas H Inge, Carroll M Harmon, Amit Ghoshal, Zengru Wu, Michael J McPhaul, Farid Saad, Paresh Dandona High prevalence of subnormal testosterone in obese adolescent males: reversal with bariatric surgery. *Eur J Endocrinol*. (2022 Feb 1)
- 21. Niansheng Tang, Bin Yu Bayesian sample size determination in a three-arm non-inferiority trial with binary endpoints. *J Biopharm Stat*. (2022 Feb 25)
- 22. Ryan Ian Houe Chong, Clyve Yu Leon Yaow, Caitlin Yuen Ling Loh, Seth En Teoh, Yoshio Masuda, Wee Khoon Ng, Yu Liang Lim, Qin Xiang Ng Vitamin D supplementation for irritable bowel syndrome: A systematic review and meta-analysis. *J Gastroenterol Hepatol*. (2022 Apr 8)
- 23. Anders Gudiksen, Albina Qoqaj, Stine Ringholm, Jørgen Wojtaszewski, Peter Plomgaard, Henriette Pilegaard Ameliorating effects of lifelong physical activity on healthy aging and mitochondrial function in human white adipose tissue. *J Gerontol A Biol Sci Med Sci*. (2021 Dec 7)
- 24. Hai Duc Nguyen, Hojin Oh, Min-Sun Kim An increased intake of nutrients, fruits, and green vegetables was negatively related to the risk of arthritis and osteoarthritis development in the aging population. *Nutr Res.* (2022 Mar)
- 25. Emma Ruby Francis, Dorina Cadar, Andrew Steptoe, Olesya Ajnakina Interplay between polygenic propensity for ageing-related traits and the consumption of fruits and vegetables on future dementia diagnosis. *BMC Psychiatry*. (2022 Jan 30)
- 26. Poorna Gopal Azad Sreeramaneni, Amulya Yalamanchi, Manikyeswara Rao Konda, Sree Harsha Varma Cherukuri, Joseph C Maroon A Proprietary Herbal Blend Containing Extracts of Punica granatum Fruit Rind and Theobroma cocoa Seeds Increases Serum Testosterone Level in Healthy Young Males: A Randomized, Double-Blind Placebo-Controlled Study. *J Diet Suppl*. (2022 Feb 6)
- 27. Mehnoosh Samadi, Mehdi Moradinazar, Tina Khosravy, Davood Soleimani, Parvin Jahangiri, Negin Kamari A systematic review and meta-analysis of preclinical and clinical studies on the efficacy of ginger for the treatment of fatty liver disease. *Phytother Res.* (2022 Mar)
- 28. Zhixin Zhu, Xiaoxia Zhu, Lanfang Gu, Yancen Zhan, Liang Chen, Xiuyang Li Association Between Vitamin D and Influenza: Meta-Analysis and Systematic Review of Randomized Controlled Trials. *Front Nutr.* (2022 Jan 7)
- 29. Azizullah Beran, Mohammed Mhanna, Omar Srour, Hazem Ayesh, Jamie M Stewart, Majdal Hjouj,

Waleed Khokher, Asmaa S Mhanna, Dana Ghazaleh, Yasmin Khader, Wasef Sayeh, Ragheb Assaly Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: A comprehensive systematic review and meta-analysis. *Clin Nutr ESPEN*. (2022 Apr)

- 30. Mona A Abdelrahman, Hasnaa Osama, Haitham Saeed, Yasmin M Madney, Hadeer S Harb, Mohamed E A Abdelrahim Impact of n-3 polyunsaturated fatty acid intake in pregnancy on maternal health and birth outcomes: systematic review and meta-analysis from randomized controlled trails. *Arch Gynecol Obstet*. (2022 Mar 28)
- 31. Ya-Hui Shih, Hsin-Chuan Wu, Wen-Harn Pan, Hsing-Yi Chang The Association Between Frequent Sugar-Sweetened Beverage Intake and Sleep Duration in School Children: A Cross-Sectional Study. *Front Nutr*. (2022 Mar 15)
- 32. Nicklas Brustad, Sina Yousef, Jakob Stokholm, Klaus Bønnelykke, Hans Bisgaard, Bo Lund Chawes Safety of High-Dose Vitamin D Supplementation Among Children Aged 0 to 6 Years: A Systematic Review and Meta-analysis. *JAMA Netw Open*. (2022 Apr 1)
- 33. Xiaoqin Luo, Wanyu Zhang, Zhangya He, Hexiang Yang, Jiayi Gao, Pei Wu, Zheng Feei Ma Dietary Vitamin C Intake Is Associated With Improved Liver Function and Glucose Metabolism in Chinese Adults. *Front Nutr*. (2022 Jan 31)
- 34. Ann M Farrell, Dianna J Magliano, Jonathan E Shaw, Alexander J Thompson, Catherine Croagh, Marno C Ryan, Jessica Howell A problem of proportions: estimates of metabolic associated fatty liver disease and liver fibrosis in Australian adults in the nationwide 2012 AusDiab Study. Sci Rep. (2022 Feb 4)
- 35. Yang Xia, Limin Cao, Qing Zhang, Li Liu, Shunming Zhang, Ge Meng, Hongmei Wu, Yeqing Gu, Shaomei Sun, Xing Wang, Ming Zhou, Qiyu Jia, Kun Song, Qijun Wu, Kaijun Niu, Yuhong Zhao Adherence to a vegetable dietary pattern attenuates the risk of non-alcoholic fatty liver disease in incident type 2 diabetes: The TCLSIH cohort study. *J Intern Med*. (2022 Apr)
- 36. Arpan Jain, Barjesh Chander Sharma, Bhawna Mahajan, Siddharth Srivastava, Ajay Kumar, Sanjeev Sachdeva, Ujjwal Sonika, Ashok Dalal L-ornithine L-aspartate in acute treatment of severe hepatic encephalopathy: A double-blind randomized controlled trial. *Hepatology*. (2022 May)
- 37. Yi Tang, Xu Chen, Qian Chen, Jinghe Xiao, Jiaxin Mi, Qiannan Liu, Yiran You, Yuming Chen, Wenhua Ling Association of serum methionine metabolites with non-alcoholic fatty liver disease: a cross-sectional study. *Nutr Metab (Lond)*. (2022 Mar 18)
- 38. Waseem Amjad, Paul Thuluvath, Muhammad Mansoor, Abhishek Dutta, Farman Ali, Waqas Qureshi N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies. *Prz Gastroenterol*. (2022)
- 39. Nadine B Wachsmuth, Felix Aberer, Sandra Haupt, Janis R Schierbauer, Rebecca T Zimmer, Max L Eckstein, Beate Zunner, Walter Schmidt, Tobias Niedrist, Harald Sourij, Othmar Moser The Impact

of a High-Carbohydrate/Low Fat vs. Low-Carbohydrate Diet on Performance and Body Composition in Physically Active Adults: A Cross-Over Controlled Trial. *Nutrients*. (2022 Jan 18)

- 40. Giovanni Antonio Silverii, Claudia Cosentino, Federica Santagiuliana, Francesco Rotella, Federica Benvenuti, Edoardo Mannucci, Barbara Cresci Effectiveness of Low Carbohydrate diets for longterm weight loss in obese individuals: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. (2022 Apr 4)
- 41. Andreas Kortenkamp, Olwenn Martin, Sibylle Ermler, Asma Baig, Martin Scholze Bisphenol A and declining semen quality: A systematic review to support the derivation of a reference dose for mixture risk assessments. *Int J Hyg Environ Health*. (2022 Apr)
- 42. Shahin Minaei, Morteza Jourkesh, Richard B Kreider, Scott C Forbes, Tacito P Souza-Junior, Steven R McAnulty, Douglas Kalman CYP1A2 Genotype Polymorphism Influences the Effect of Caffeine on Anaerobic Performance in Trained Males. *Int J Sport Nutr Exerc Metab*. (2022 Jan 1)
- 43. Gregory C Bogdanis, Mary E Nevill, George Aphamis, Pinelopi S Stavrinou, David G Jenkins, Christoforos D Giannaki, Henryk K A Lakomy, Clyde Williams Effects of Oral Creatine Supplementation on Power Output during Repeated Treadmill Sprinting. Nutrients. (2022 Mar 8)
- 44. Claudia Hartley, Amelia Carr, Steven J Bowe, Wender L P Bredie, Russell S J Keast Maltodextrin-Based Carbohydrate Oral Rinsing and Exercise Performance: Systematic Review and Meta-Analysis. Sports Med. (2022 Mar 3)
- 45. Katieli Santos de Lima, Felipe Barreto Schuch, Natiele Camponogara Righi, Patricia Chagas, Mireli Hemann Lamberti, Gustavo Orione Puntel, Antonio Marcos Vargas da Silva, Luis Ulisses Signori Effects of the combination of vitamins C and E supplementation on oxidative stress, inflammation, muscle soreness, and muscle strength following acute physical exercise: metaanalyses of randomized controlled trials. *Crit Rev Food Sci Nutr*. (2022 Mar 9)
- 46. Asier Santibañez-Gutierrez, Julen Fernández-Landa, Julio Calleja-González, Anne Delextrat, Juan Mielgo-Ayuso Effects of Probiotic Supplementation on Exercise with Predominance of Aerobic Metabolism in Trained Population: A Systematic Review, Meta-Analysis and Meta-Regression. Nutrients. (2022 Jan 30)
- 47. Ayano Hiratsu, Yusei Tataka, Saki Namura, Chihiro Nagayama, Yuka Hamada, Masashi Miyashita The effects of acute and chronic oral l-arginine supplementation on exercise-induced ammonia accumulation and exercise performance in healthy young men: A randomised, double-blind, cross-over, placebo-controlled trial. *J Exerc Sci Fit*. (2022 Apr)
- 48. Yutan Wang, Hongmei Lu, Sijun Li, Yuanyuan Zhang, Fanghong Yan, Yanan Huang, Xiaoli Chen, Ailing Yang, Lin Han, Yuxia Ma Effect of cold and heat therapies on pain relief in patients with delayed onset muscle soreness: A network meta-analysis. *J Rehabil Med*. (2022 Feb 8)
- 49. Christiane Schön, Katharina Knaub, Wilfried Alt, Shane Durkee, Zainulabedin Saiyed, Vijaya

Juturu UC-II Undenatured Type II Collagen for Knee Joint Flexibility: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study. *J Integr Complement Med*. (2022 Apr 4)

- 50. James Meixiong, Cristina Ricco, Chirag Vasavda, Byron K Ho Diet and acne: A systematic review. JAAD Int. (2022 Mar 29)
- 51. Selicia T Mayra, Carol S Johnston Arterial stiffness and cardiometabolic health in omnivores and vegetarians: a cross-sectional pilot study. *BMC Res Notes*. (2022 Feb 19)
- 52. Agnes Valim, Larissa Salomoni Carpes, Bruna Bellincanta Nicoletto Effect of vegetarian diets on renal function in patients with chronic kidney disease under non-dialysis treatment: A scoping review. *J Bras Nefrol*. (2022 Jan 31)
- 53. Fayth L Miles, Michael J Orlich, Andrew Mashchak, Paulette D Chandler, Johanna W Lampe, Penelope Duerksen-Hughes, Gary E Fraser The Biology of Veganism: Plasma Metabolomics Analysis Reveals Distinct Profiles of Vegans and Non-Vegetarians in the Adventist Health Study-2 Cohort. Nutrients. (2022 Feb 8)
- 54. Winston J Craig, A Reed Mangels, Cecilia J Brothers Nutritional Profiles of Non-Dairy Plant-Based Cheese Alternatives. *Nutrients*. (2022 Mar 16)
- 55. Yu-Min He, Wei-Liang Chen, Tung-Wei Kao, Li-Wei Wu, Hui-Fang Yang, Tao-Chun Peng Association Between Ideal Cardiovascular Health and Vegetarian Dietary Patterns Among Community-Dwelling Individuals. *Front Nutr*. (2022 Mar 18)

## References

- 1. Brad J Schoenfeld, Dan Ogborn, James W Krieger Dose-response Relationship Between Weekly Resistance Training Volume and Increases in Muscle Mass: A Systematic Review and Meta-Analysis. *J Sports Sci*. (2017 Jun)
- 2. Eneko Baz-Valle, Maelán Fontes-Villalba, Jordan Santos-Concejero Total Number of Sets as a Training Volume Quantification Method for Muscle Hypertrophy: A Systematic Review. *J Strength Cond Res.* (2021 Mar 1)
- Lucas Brandão, Vitor de Salles Painelli, Thiago Lasevicius, Carla Silva-Batista, Helderson Brendon, Brad Jon Schoenfeld, André Yui Aihara, Fabiano Nassar Cardoso, Bergson de Almeida Peres, Emerson Luiz Teixeira Varying the Order of Combinations of Single- and Multi-Joint Exercises Differentially Affects Resistance Training Adaptations. J Strength Cond Res. (2020 May)
- Maíra C Scarpelli, Sanmy R Nóbrega, Natalia Santanielo, Ieda F Alvarez, Gabriele B Otoboni, Carlos Ugrinowitsch, Cleiton A Libardi Muscle Hypertrophy Response Is Affected by Previous Resistance Training Volume in Trained Individuals. J Strength Cond Res. (2022 Apr 1)

- Vitor Angleri, Carlos Ugrinowitsch, Cleiton Augusto Libardi Crescent pyramid and drop-set systems do not promote greater strength gains, muscle hypertrophy, and changes on muscle architecture compared with traditional resistance training in well-trained men. *Eur J Appl Physiol*. (2017 Feb)
- 6. Panday A, Sahoo MK, Osorio D, Batra S NADPH oxidases: an overview from structure to innate immunity-associated pathologies. *Cell Mol Immunol.* (2015 Jan)
- Jessica Bouviere, Rodrigo S Fortunato, Corinne Dupuy, Joao Pedro Werneck-de-Castro, Denise P Carvalho, Ruy A Louzada Exercise-Stimulated ROS Sensitive Signaling Pathways in Skeletal Muscle. Antioxidants (Basel). (2021 Mar 30)
- 8. Cobley JN, Close GL, Bailey DM, Davison GW Exercise redox biochemistry: Conceptual, methodological and technical recommendations. *Redox Biol*. (2017 Aug)
- 9. Helmut Sies Oxidative eustress: On constant alert for redox homeostasis. Redox Biol. (2021 May)
- 10. Minna Tanskanen, Mustafa Atalay, Arja Uusitalo Altered oxidative stress in overtrained athletes. *J Sports Sci.* (2010 Feb)
- 11. Érica Cerqueira, Daniel A Marinho, Henrique P Neiva, Olga Lourenço Inflammatory Effects of High and Moderate Intensity Exercise-A Systematic Review. *Front Physiol*. (2020 Jan 9)
- 12. Anand Thirupathi, Yaodong Gu, Ricardo Aurino Pinho Exercise Cuts Both Ways with ROS in Remodifying Innate and Adaptive Responses: Rewiring the Redox Mechanism of the Immune System during Exercise. *Antioxidants (Basel)*. (2021 Nov 21)
- 13. Krasimira Aleksandrova, Liselot Koelman, Caue Egea Rodrigues Dietary patterns and biomarkers of oxidative stress and inflammation: A systematic review of observational and intervention studies. *Redox Biol.* (2021 Jun)
- 14. Ilaria Marrocco, Fabio Altieri, Ilaria Peluso Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. Oxid Med Cell Longev. (2017)
- 15. Karen M O'Callaghan, Daniel E Roth Standardization of laboratory practices and reporting of biomarker data in clinical nutrition research. *Am J Clin Nutr*. (2020 Aug 1)
- 16. R Xu, N Liu, X Xu, B Kong Antioxidative effects of whey protein on peroxide-induced cytotoxicity. *J Dairy Sci.* (2011 Aug)
- Hossam Ebaid, Amir Salem, Abdalla Sayed, Ali Metwalli Whey protein enhances normal inflammatory responses during cutaneous wound healing in diabetic rats. *Lipids Health Dis*. (2011 Dec 14)
- 18. Efthalia Kerasioti, Dimitrios Stagos, Athanasios Jamurtas, Alexandra Kiskini, Yiannis Koutedakis, Nikos Goutzourelas, Spyros Pournaras, Aristidis M Tsatsakis, Dimitrios Kouretas Anti-

inflammatory effects of a special carbohydrate-whey protein cake after exhaustive cycling in humans. *Food Chem Toxicol*. (2013 Nov)

- Gøran Paulsen, Kristoffer T Cumming, Geir Holden, Jostein Hallén, Bent Ronny Rønnestad, Ole Sveen, Arne Skaug, Ingvild Paur, Nasser E Bastani, Hege Nymo Østgaard, Charlotte Buer, Magnus Midttun, Fredrik Freuchen, Havard Wiig, Elisabeth Tallaksen Ulseth, Ina Garthe, Rune Blomhoff, Haakon B Benestad, Truls Raastad Vitamin C and E supplementation hampers cellular adaptation to endurance training in humans: a double-blind, randomised, controlled trial. *J Physiol*. (2014 Apr 15)
- 20. Tom Clifford, Owen Jeffries, Emma J Stevenson, Kelly A Bowden Davies The effects of vitamin C and E on exercise-induced physiological adaptations: a systematic review and Meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. (2020)
- 21. Cristina Canals-Garzón, Rafael Guisado-Barrilao, Darío Martínez-García, Ignacio Jesús Chirosa-Ríos, Daniel Jerez-Mayorga, Isabel María Guisado-Requena Effect of Antioxidant Supplementation on Markers of Oxidative Stress and Muscle Damage after Strength Exercise: A Systematic Review. *Int J Environ Res Public Health*. (2022 Feb 5)
- 22. Mayur K Ranchordas, David Rogerson, Hora Soltani, Joseph T Costello Antioxidants for preventing and reducing muscle soreness after exercise: a Cochrane systematic review. *Br J Sports Med*. (2020 Jan)
- 23. Connor M Sheehan, Stephen E Frochen, Katrina M Walsemann, Jennifer A Ailshire Are U.S. adults reporting less sleep?: Findings from sleep duration trends in the National Health Interview Survey, 2004-2017. *Sleep*. (2019 Feb 1)
- 24. Earl S Ford, Timothy J Cunningham, Wayne H Giles, Janet B Croft Trends in insomnia and excessive daytime sleepiness among U.S. adults from 2002 to 2012. *Sleep Med*. (2015 Mar)
- 25. Daniel F Kripke Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. *F1000Res*. (2016 May 19)
- 26. Zhila Taherzadeh, Hosein Khaluyan, Milad Iranshahy, Fariborz Rezaeitalab, Mohammad Hosein Eshaghi Ghalibaf, Behjat Javadi Evaluation of sedative effects of an intranasal dosage form containing saffron, lettuce seeds and sweet violet in primary chronic insomnia: A randomized, double-dummy, double-blind placebo controlled clinical trial. *J Ethnopharmacol*. (2020 Jul 28)
- 27. Lucy M McDonnell, Lauren Hogg, Lynn McDonnell, Patrick White Pulmonary rehabilitation and sleep quality: a before and after controlled study of patients with chronic obstructive pulmonary disease. *NPJ Prim Care Respir Med*. (2014 Jul 10)
- 28. Ciara M Hughes, Carey A McCullough, Ian Bradbury, Carol Boyde, Diane Hume, Jiang Yuan, Fionnuala Quinn, Suzanne M McDonough Acupuncture and reflexology for insomnia: a feasibility study. Acupunct Med. (2009 Dec)

- 29. Michael Paul Foley, Scott Michael Hasson, Eydie Kendall Effects of a Translational Community-Based Multimodal Exercise Program on Quality of Life and the Influence of Start Delay on Physical Function and Quality of Life in Breast Cancer Survivors: A Pilot Study. *Integr Cancer Ther*. (2018 Jun)
- 30. Umile Giuseppe Longo, Alessandra Berton, Sergio De Salvatore, Ilaria Piergentili, Erica Casciani, Aurora Faldetta, Maria Grazia De Marinis, Vincenzo Denaro Minimal Clinically Important Difference and Patient Acceptable Symptom State for the Pittsburgh Sleep Quality Index in Patients Who Underwent Rotator Cuff Tear Repair. Int J Environ Res Public Health. (2021 Aug 17)
- 31. Dongming Wang, Wenzhen Li, Xiuqing Cui, Yidi Meng, Min Zhou, Lili Xiao, Jixuan Ma, Guilin Yi, Weihong Chen Sleep duration and risk of coronary heart disease: A systematic review and metaanalysis of prospective cohort studies. *Int J Cardiol*. (2016 Sep 15)
- 32. Sizhi Ai, Jihui Zhang, Guoan Zhao, Ningjian Wang, Guohua Li, Hon-Cheong So, Yaping Liu, Steven Wai-Ho Chau, Jie Chen, Xiao Tan, Fujun Jia, Xiangdong Tang, Jie Shi, Lin Lu, Yun-Kwok Wing Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and nonlinear Mendelian randomization analyses in UK Biobank. *Eur Heart J*. (2021 Sep 7)
- 33. Qionggui Zhou, Ming Zhang, Dongsheng Hu Dose-response association between sleep duration and obesity risk: a systematic review and meta-analysis of prospective cohort studies. *Sleep Breath*. (2019 Dec)
- 34. Francesco P Cappuccio, Frances M Taggart, Ngianga-Bakwin Kandala, Andrew Currie, Ed Peile, Saverio Stranges, Michelle A Miller Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. (2008 May)
- 35. Bingqian Zhu, Changgui Shi, Chang G Park, Xiangxiang Zhao, Sirimon Reutrakul Effects of sleep restriction on metabolism-related parameters in healthy adults: A comprehensive review and meta-analysis of randomized controlled trials. *Sleep Med Rev.* (2019 Jun)
- 36. Esra Tasali, Kristen Wroblewski, Eva Kahn, Jennifer Kilkus, Dale A Schoeller Effect of Sleep Extension on Objectively Assessed Energy Intake Among Adults With Overweight in Real-life Settings: A Randomized Clinical Trial. *JAMA Intern Med*. (2022 Feb 7)
- Omonigho M Bubu, Michael Brannick, James Mortimer, Ogie Umasabor-Bubu, Yuri V Sebastião, Yi Wen, Skai Schwartz, Amy R Borenstein, Yougui Wu, David Morgan, William M Anderson Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. *Sleep*. (2017 Jan 1)
- 38. Jeffrey J Iliff, Minghuan Wang, Yonghong Liao, Benjamin A Plogg, Weiguo Peng, Georg A Gundersen, Helene Benveniste, G Edward Vates, Rashid Deane, Steven A Goldman, Erlend A Nagelhus, Maiken Nedergaard A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. (2012)

Aug 15)

- Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M Sleep drives metabolite clearance from the adult brain. *Science*. (2013 Oct 18)
- 40. Zhilei Shan, Hongfei Ma, Manling Xie, Peipei Yan, Yanjun Guo, Wei Bao, Ying Rong, Chandra L Jackson, Frank B Hu, Liegang Liu Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care*. (2015 Mar)
- 41. Xue Gao, Heli Sun, Yu Zhang, Long Liu, Juping Wang, Tong Wang Investigating Causal Relations Between Sleep-Related Traits and Risk of Type 2 Diabetes Mellitus: A Mendelian Randomization Study. *Front Genet*. (2020 Dec 15)
- 42. Feng Pan, Jing Tian, Flavia Cicuttini, Graeme Jones Sleep disturbance and bone mineral density, risk of falls and fracture: Results from a 10.7-year prospective cohort study. *Bone*. (2021 Jun)
- 43. Yu Qian, Jiangwei Xia, Ke-Qi Liu, Lin Xu, Shu-Yang Xie, Guo-Bo Chen, Pei-Kuan Cong, Saber Khederzadeh, Hou-Feng Zheng Observational and genetic evidence highlight the association of human sleep behaviors with the incidence of fracture. *Commun Biol*. (2021 Nov 26)
- 44. Jane A Cauley, Kathleen M Hovey, Katie L Stone, Chris A Andrews, Kamil E Barbour, Lauren Hale, Rebecca D Jackson, Karen C Johnson, Erin S LeBlanc, Wenjun Li, Oleg Zaslavsky, Heather Ochs-Balcom, Jean Wactawski-Wende, Carolyn J Crandall Characteristics of Self-Reported Sleep and the Risk of Falls and Fractures: The Women's Health Initiative (WHI). J Bone Miner Res. (2019 Mar)
- 45. Liqing Li, Chunmei Wu, Yong Gan, Xianguo Qu, Zuxun Lu Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC Psychiatry*. (2016 Nov 5)
- 46. W Vaughn McCall, Jill N Blocker, Ralph D'Agostino Jr, James Kimball, Niki Boggs, Barbara Lasater, Roger Haskett, Andrew Krystal, William M McDonald, Peter B Rosenquist Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression. J Clin Sleep Med. (2010 Aug 15)
- 47. Maurizio Fava, W Vaughn McCall, Andrew Krystal, Thomas Wessel, Robert Rubens, Judy Caron, David Amato, Thomas Roth Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry*. (2006 Jun 1)
- 48. Rachel Manber, Jack D Edinger, Jenna L Gress, Melanie G San Pedro-Salcedo, Tracy F Kuo, Tasha Kalista Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep*. (2008 Apr)
- 49. YongMin Cho, Seung-Hun Ryu, Byeo Ri Lee, Kyung Hee Kim, Eunil Lee, Jaewook Choi Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int*. (2015)

- 50. Esaki Y, Kitajima T, Ito Y, Koike S, Nakao Y, Tsuchiya A, Hirose M, Iwata N Wearing blue lightblocking glasses in the evening advances circadian rhythms in the patients with delayed sleep phase disorder: An open-label trial. *Chronobiol Int*. (2016)
- 51. Heo JY, Kim K, Fava M, Mischoulon D, Papakostas GI, Kim MJ, Kim DJ, Chang KJ, Oh Y, Yu BH, Jeon HJ Effects of smartphone use with and without blue light at night in healthy adults: A randomized, double-blind, cross-over, placebo-controlled comparison. *J Psychiatr Res.* (2017 Apr)
- 52. Kovacevic A, Mavros Y, Heisz JJ, Fiatarone Singh MA The effect of resistance exercise on sleep: A systematic review of randomized controlled trials. *Sleep Med Rev.* (2018 Jun)
- 53. Hartescu I, Morgan K, Stevinson CD Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. *J Sleep Res.* (2015 Oct)
- 54. Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Med*. (2010 Oct)
- 55. Drake C, Roehrs T, Shambroom J, Roth T Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med*. (2013 Nov 15)
- 56. Clark I, Landolt HP Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev.* (2017 Feb)
- Adrian L Lopresti, Peter D Drummond, Antonio M Inarejos-García, Marin Prodanov affron<sup>®</sup>, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. *J Affect Disord*. (2018 May)
- 58. Alireza Milajerdi, Shima Jazayeri, Elham Shirzadi, Najmeh Hashemzadeh, Atieh Azizgol, Abolghassem Djazayery, Ahmad Esmaillzadeh, Shahin Akhondzadeh The effects of alcoholic extract of saffron (Crocus satious L.) on mild to moderate comorbid depression-anxiety, sleep quality, and life satisfaction in type 2 diabetes mellitus: A double-blind, randomized and placebocontrolled clinical trial. *Complement Ther Med*. (2018 Dec)
- Anahita Khalatbari-Mohseni, Hamid Reza Banafshe, Naghmeh Mirhosseini, Zatollah Asemi, Amir Ghaderi, Abdollah Omidi The effects of crocin on psychological parameters in patients under methadone maintenance treatment: a randomized clinical trial. Subst Abuse Treat Prev Policy. (2019 Feb 22)
- 60. Chang-Myung Oh, Ha Yan Kim, Han Kyu Na, Kyoo Ho Cho, Min Kyung Chu The Effect of Anxiety and Depression on Sleep Quality of Individuals With High Risk for Insomnia: A Population-Based Study. *Front Neurol*. (2019 Aug 13)
- 61. Adrian L Lopresti, Stephen J Smith, Peter D Drummond An investigation into an evening intake of a saffron extract (affron®) on sleep quality, cortisol, and melatonin concentrations in adults with

poor sleep: a randomised, double-blind, placebo-controlled, multi-dose study. *Sleep Med*. (2021 Oct)

- I M Stratton, A I Adler, H A Neil, D R Matthews, S E Manley, C A Cull, D Hadden, R C Turner, R R Holman Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. (2000 Aug 12)
- 63. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. (1998 Sep 12)
- 64. Fengyi Zhao, Da Pan, Niannian Wang, Hui Xia, Hong Zhang, Shaokang Wang, Guiju Sun Effect of Chromium Supplementation on Blood Glucose and Lipid Levels in Patients with Type 2 Diabetes Mellitus: a Systematic Review and Meta-analysis. *Biol Trace Elem Res*. (2022 Feb)
- 65. Shi-Ying Zhang, Kai-Lin Yang, Liu-Ting Zeng, Xiao-He Wu, Hui-Yong Huang Effectiveness of Coenzyme Q10 Supplementation for Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Int J Endocrinol*. (2018 Sep 16)
- 66. Ashor AW, Werner AD, Lara J, Willis ND, Mathers JC, Siervo M Effects of vitamin C supplementation on glycaemic control: a systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Nutr*. (2017 Dec)
- 67. Bland JM, Altman DG Comparisons against baseline within randomised groups are often used and can be highly misleading. *Trials*. (2011 Dec 22)
- 68. David S Ludwig, Louis J Aronne, Arne Astrup, Rafael de Cabo, Lewis C Cantley, Mark I Friedman, Steven B Heymsfield, James D Johnson, Janet C King, Ronald M Krauss, Daniel E Lieberman, Gary Taubes, Jeff S Volek, Eric C Westman, Walter C Willett, William S Yancy, Cara B Ebbeling The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. *Am J Clin Nutr*. (2021 Sep 13)
- 69. K Evans, M L Clark, K N Frayn Effects of an oral and intravenous fat load on adipose tissue and forearm lipid metabolism. *Am J Physiol*. (1999 Feb)
- 70. J S Samra, S L Giles, L K Summers, R D Evans, P Arner, S M Humphreys, M L Clark, K N Frayn Peripheral fat metabolism during infusion of an exogenous triacylglycerol emulsion. *Int J Obes Relat Metab Disord*. (1998 Aug)
- 71. Asem H Ali, Manpreet Mundi, Christina Koutsari, David A Bernlohr, Michael D Jensen Adipose Tissue Free Fatty Acid Storage In Vivo: Effects of Insulin Versus Niacin as a Control for Suppression of Lipolysis. *Diabetes*. (2015 Aug)
- 72. S W Coppack, K N Frayn, S M Humphreys Plasma triacylglycerol extraction in human adipose tissue in vivo: effects of glucose ingestion and insulin infusion. *Eur J Clin Nutr*. (1989 Jul)

- 73. André C Carpentier 100 th anniversary of the discovery of insulin perspective: insulin and adipose tissue fatty acid metabolism. *Am J Physiol Endocrinol Metab*. (2021 Apr 1)
- 74. Institute of Medicine (US) Committee on Sleep Medicine and Research, Harvey R Colten, Bruce M Altevogt Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem.
- 75. Siaw Cheok Liew, Thidar Aung Sleep deprivation and its association with diseases- a review. *Sleep Med*. (2021 Jan)
- 76. Giovanna Muscogiuri, Luigi Barrea, Marianna Scannapieco, Carolina Di Somma, Massimo Scacchi, Gianluca Aimaretti, Silvia Savastano, Annamaria Colao, Paolo Marzullo The lullaby of the sun: the role of vitamin D in sleep disturbance. *Sleep Med*. (2019 Feb)
- 77. Qi Gao, Tingyan Kou, Bin Zhuang, Yangyang Ren, Xue Dong, Qiuzhen Wang The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. *Nutrients*. (2018 Oct 1)
- 78. Juliana Rombaldi Bernardi, Renata de Souza Escobar, Charles Francisco Ferreira, Patrícia Pelufo Silveira Fetal and neonatal levels of omega-3: effects on neurodevelopment, nutrition, and growth. *ScientificWorldJournal*. (2012)
- 79. Michael J Weiser, Christopher M Butt, M Hasan Mohajeri Docosahexaenoic Acid and Cognition throughout the Lifespan. *Nutrients*. (2016 Feb 17)
- 80. Zofia Barcikowska, Elżbieta Rajkowska-Labon, Magdalena Emilia Grzybowska, Rita Hansdorfer-Korzon, Katarzyna Zorena Inflammatory Markers in Dysmenorrhea and Therapeutic Options. *Int J Environ Res Public Health*. (2020 Feb 13)
- 81. Laleh Payahoo, Yaser Khajebishak, Mohammad Asghari Jafarabadi, Alireza Ostadrahimi Oleoylethanolamide Supplementation Reduces Inflammation and Oxidative Stress in Obese People: A Clinical Trial. *Adv Pharm Bull*. (2018 Aug)
- 82. Wenjie Jian, Ka-Chai Siu, Jian-Yong Wu Effects of pH and temperature on colloidal properties and molecular characteristics of Konjac glucomannan. *Carbohydr Polym*. (2015 Dec 10)
- 83. Grethe Støa Birketvedt, Mona Shimshi, Thom Erling, Jon Florholmen Experiences with three different fiber supplements in weight reduction. *Med Sci Monit*. (2005 Jan)
- 84. Bartłomiej M Zalewski, Anna Chmielewska, Hania Szajewska The effect of glucomannan on body weight in overweight or obese children and adults: a systematic review of randomized controlled trials. *Nutrition*. (2015 Mar)
- 85. Nitesh Sood, William L Baker, Craig I Coleman Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. *Am J Clin Nutr*. (2008 Oct)

- Hsiao-Ling Chen, Han-Chung Cheng, Wen-Tsu Wu, Yann-Jiu Liu, Su-Yuan Liu Supplementation of konjac glucomannan into a low-fiber Chinese diet promoted bowel movement and improved colonic ecology in constipated adults: a placebo-controlled, diet-controlled trial. *J Am Coll Nutr*. (2008 Feb)
- 87. David G King, Mark Walker, Matthew D Campbell, Leigh Breen, Emma J Stevenson, Daniel J West A small dose of whey protein co-ingested with mixed-macronutrient breakfast and lunch meals improves postprandial glycemia and suppresses appetite in men with type 2 diabetes: a randomized controlled trial. *Am J Clin Nutr*. (2018 Apr 1)
- 88. Anni Larnkjær, Karina Arnberg, Kim F Michaelsen, Signe M Jensen, Christian Mølgaard Effect of milk proteins on linear growth and IGF variables in overweight adolescents. Growth Horm IGF Res. (Apr-Jun 2014)
- 89. C Hoppe, C Mølgaard, C Dalum, A Vaag, K F Michaelsen Differential effects of casein versus whey on fasting plasma levels of insulin, IGF-1 and IGF-1/IGFBP-3: results from a randomized 7-day supplementation study in prepubertal boys. *Eur J Clin Nutr*. (2009 Sep)
- 90. S Sasidharan, Y Chen, D Saravanan, K M Sundram, L Yoga Latha Extraction, isolation and characterization of bioactive compounds from plants' extracts. *Afr J Tradit Complement Altern Med*. (2011)
- 91. Giuseppe Caruso, Justyna Godos, Anna Privitera, Giuseppe Lanza, Sabrina Castellano, Alessio Chillemi, Oliviero Bruni, Raffaele Ferri, Filippo Caraci, Giuseppe Grosso Phenolic Acids and Prevention of Cognitive Decline: Polyphenols with a Neuroprotective Role in Cognitive Disorders and Alzheimer's Disease. *Nutrients*. (2022 Feb 15)
- Daniel Joseph Lamport, Claire Michelle Williams Polyphenols and Cognition In Humans: An Overview of Current Evidence from Recent Systematic Reviews and Meta-Analyses. Brain Plast. (2021 Feb 9)
- 93. Christine Morand, Francisco A Tomás-Barberán Contribution of plant food bioactives in promoting health effects of plant foods: why look at interindividual variability?. *Eur J Nutr*. (2019 Nov)
- 94. Christine Morand, Francisco A Tomás-Barberán Interindividual Variability in Absorption, Distribution, Metabolism, and Excretion of Food Phytochemicals Should Be Reported. *J Agric Food Chem*. (2019 Apr 10)
- 95. Christine Morand, Baukje De Roos, Maria Teresa Garcia-Conesa, Eileen R Gibney, Rikard Landberg, Claudine Manach, Dragan Milenkovic, Ana Rodriguez-Mateos, Tom Van de Wiele, Francisco Tomas-Barberan Why interindividual variation in response to consumption of plant food bioactives matters for future personalised nutrition. *Proc Nutr Soc*. (2020 May)
- 96. Bohn T Dietary factors affecting polyphenol bioavailability. Nutr Rev. (2014 Jul)

- 97. Inês Figueira, Lucélia Tavares, Carolina Jardim, Inês Costa, Ana P Terrasso, Andreia F Almeida, Coen Govers, Jurriaan J Mes, Rui Gardner, Jörg D Becker, Gordon J McDougall, Derek Stewart, Augusto Filipe, Kwang S Kim, Dora Brites, Catarina Brito, M Alexandra Brito, Cláudia N Santos Blood-brain Barrier Transport and Neuroprotective Potential of Blackberry-Digested Polyphenols: An in Vitro Study. Eur J Nutr. (2019 Feb)
- 98. Rena Shimazu, Moemi Anada, Amane Miyaguchi, Yuri Nomi, Hitoshi Matsumoto Evaluation of Blood-Brain Barrier Permeability of Polyphenols, Anthocyanins, and Their Metabolites. *J Agric Food Chem*. (2021 Oct 6)
- 99. Mengchi Li, Hyejin Kim, Susan M Sereika, Trevor J Nissley, Jennifer H Lingler Willingness to Participate in Clinical Research Among Individuals With Cognitive Impairment. *Res Gerontol Nurs*. (Mar-Apr 2022)
- 100. Jamie Gahche, Regan Bailey, Vicki Burt, Jeffery Hughes, Elizabeth Yetley, Johanna Dwyer, Mary Frances Picciano, Margaret McDowell, Christopher Sempos Dietary supplement use among U.S. adults has increased since NHANES III (1988-1994). NCHS Data Brief. (2011 Apr)
- 101. Stephen P Fortmann, Brittany U Burda, Caitlyn A Senger, Jennifer S Lin, Tracy L Beil, Elizabeth O'Connor, Evelyn P Whitlock Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force Internet.
- 102. Blumberg JB, Cena H, Barr SI, Biesalski HK, Dagach RU, Delaney B, Frei B, Moreno González MI, Hwalla N, Lategan-Potgieter R, McNulty H, van der Pols JC, Winichagoon P, Li D The Use of Multivitamin/Multimineral Supplements: A Modified Delphi Consensus Panel Report. Clin Ther. (2018 Apr)
- 103. J Michael Gaziano, Howard D Sesso, William G Christen, Vadim Bubes, Joanne P Smith, Jean MacFadyen, Miriam Schvartz, JoAnn E Manson, Robert J Glynn, Julie E Buring Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. (2012 Nov 14)
- 104. Howard D Sesso, William G Christen, Vadim Bubes, Joanne P Smith, Jean MacFadyen, Miriam Schvartz, JoAnn E Manson, Robert J Glynn, Julie E Buring, J Michael Gaziano Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. (2012 Nov 7)
- 105. Martha Clare Morris, Christine C Tangney A potential design flaw of randomized trials of vitamin supplements. *JAMA*. (2011 Apr 6)
- 106. Serge Hercberg, Pilar Galan, Paul Preziosi, Sandrine Bertrais, Louise Mennen, Denis Malvy, Anne-Marie Roussel, Alain Favier, Serge Briançon The SU.VI.MAX Study: a randomized, placebocontrolled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. (2004

Nov 22)

- 107. Giana Angelo, Victoria J Drake, Balz Frei Efficacy of Multivitamin/mineral Supplementation to Reduce Chronic Disease Risk: A Critical Review of the Evidence from Observational Studies and Randomized Controlled Trials. *Crit Rev Food Sci Nutr*. (2015)
- 108. Joonseok Kim, Jaehyoung Choi, Soo Young Kwon, John W McEvoy, Michael J Blaha, Roger S Blumenthal, Eliseo Guallar, Di Zhao, Erin D Michos Association of Multivitamin and Mineral Supplementation and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. (2018 Jul)
- 109. Melissa Ventura Marra, Regan L Bailey Position of the Academy of Nutrition and Dietetics: Micronutrient Supplementation. *J Acad Nutr Diet*. (2018 Nov)
- 110. Hans K Biesalski, Jana Tinz Multivitamin/mineral supplements: Rationale and safety A systematic review. *Nutrition*. (2017 Jan)
- 111. Dagfinn Aune, NaNa Keum, Edward Giovannucci, Lars T Fadnes, Paolo Boffetta, Darren C Greenwood, Serena Tonstad, Lars J Vatten, Elio Riboli, Teresa Norat Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. *Am J Clin Nutr.* (2018 Nov 1)
- 112. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, Greenwood DC, Riboli E, Vatten LJ, Tonstad S Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and allcause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. (2017 Jun 1)
- 113. Ming-Chieh Tsai, Chun-Chuan Lee, Sung-Chen Liu, Po-Jung Tseng, Kuo-Liong Chien Combined healthy lifestyle factors are more beneficial in reducing cardiovascular disease in younger adults: a meta-analysis of prospective cohort studies. *Sci Rep*. (2020 Oct 23)
- 114. Choi HD, Youn YK, Shin WG Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. *Plant Foods Hum Nutr*. (2011 Nov)
- 115. Maryam Khoubnasabjafari, Khalil Ansarin, Abolghasem Jouyban Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. *Bioimpacts*. (2015)
- 116. Jozo Grgic, Craig Pickering, Juan Del Coso, Brad J Schoenfeld, Pavle Mikulic CYP1A2 genotype and acute ergogenic effects of caffeine intake on exercise performance: a systematic review. *Eur J Nutr*. (2020 Nov 2)
- 117. Palatini P, Benetti E, Mos L, Garavelli G, Mazzer A, Cozzio S, Fania C, Casiglia E Association of coffee consumption and CYP1A2 polymorphism with risk of impaired fasting glucose in hypertensive patients. *Eur J Epidemiol*. (2015 Mar)

- 118. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA*. (2006 Mar 8)
- 119. Rogerio Nogueira Soares, Augusto Schneider, Sandra Costa Valle, Paulo Cavalheiro Schenkel The influence of CYP1A2 genotype in the blood pressure response to caffeine ingestion is affected by physical activity status and caffeine consumption level. *Vascul Pharmacol*. (2018 Jul)
- 120. Palatini P, Ceolotto G, Ragazzo F, Dorigatti F, Saladini F, Papparella I, Mos L, Zanata G, Santonastaso M CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. J Hypertens. (2009 Aug)
- 121. Nanci S Guest, Trisha A VanDusseldorp, Michael T Nelson, Jozo Grgic, Brad J Schoenfeld, Nathaniel D M Jenkins, Shawn M Arent, Jose Antonio, Jeffrey R Stout, Eric T Trexler, Abbie E Smith-Ryan, Erica R Goldstein, Douglas S Kalman, Bill I Campbell International society of sports nutrition position stand: caffeine and exercise performance. J Int Soc Sports Nutr. (2021 Jan 2)
- 122. Mehran Rahimlou, Zahra Yari, Azita Hekmatdoost, Seyed Moayed Alavian, Seyed Ali Keshavarz Ginger Supplementation in Nonalcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Hepat Mon*. (2016 Jan 23)
- 123. Roya Rafie, Seyed Ahmad Hosseini, Eskandar Hajiani, Amal Saki Malehi, Seyed Ali Mard Effect of Ginger Powder Supplementation in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Clinical Trial. Clin Exp Gastroenterol. (2020 Jan 23)
- 124. Nayebi far et al The Assessment of Changes in Liver Aminotransferases and Insulin Resistance Following 4 Weeks of High Intensity Interval Training and Ginger Supplementation in Active Middle Aged Men. JSUMS. (2021)
- 125. Pierre Boutouyrie, Phil Chowienczyk, Jay D Humphrey, Gary F Mitchell Arterial Stiffness and Cardiovascular Risk in Hypertension. *Circ Res.* (2021 Apr 2)
- 126. Kristina S Petersen, Michael R Flock, Chesney K Richter, Ratna Mukherjea, Joanne L Slavin, Penny M Kris-Etherton Healthy Dietary Patterns for Preventing Cardiometabolic Disease: The Role of Plant-Based Foods and Animal Products. *Curr Dev Nutr*. (2017 Nov 6)
- 127. da Luz PL, Favarato D, Faria-Neto JR Jr, Lemos P, Chagas AC High ratio of triglycerides to HDLcholesterol predicts extensive coronary disease. *Clinics (Sao Paulo)*. (2008 Aug)
- 128. Selicia Mayra, Noel Ugarte, Carol S Johnston Health Biomarkers in Adults Are More Closely Linked to Diet Quality Attributes Than to Plant-Based Diet Categorization. *Nutrients*. (2019 Jun 25)
- 129. Hanze Chen, Beidi Zhang, Yusong Ge, Han Shi, Siqi Song, Weishuang Xue, Jinwei Li, Kailei Fu, Xinxin Chen, Weiyu Teng, Li Tian Association between skipping breakfast and risk of cardiovascular disease and all cause mortality: A meta-analysis. *Clin Nutr*. (2020 Oct)
- 130. Andrew G Renehan, Andrew Flood, Kenneth F Adams, Matthias Olden, Albert R Hollenbeck,

Amanda J Cross, Michael F Leitzmann Body mass index at different adult ages, weight change, and colorectal cancer risk in the National Institutes of Health-AARP Cohort. *Am J Epidemiol*. (2012 Dec 15)

- 131. Kenneth F Adams, Michael F Leitzmann, Rachel Ballard-Barbash, Demetrius Albanes, Tamara B Harris, Albert Hollenbeck, Victor Kipnis Body mass and weight change in adults in relation to mortality risk. *Am J Epidemiol*. (2014 Jan 15)
- 132. Berhe W Sahle, Shameran Slewa-Younan, Yohannes Adama Melaku, Li Ling, Andre M N Renzaho A bi-directional association between weight change and health-related quality of life: evidence from the 11-year follow-up of 9916 community-dwelling adults. *Qual Life Res.* (2020 Jun)
- 133. James O Hill, Holly R Wyatt, John C Peters Energy balance and obesity. *Circulation*. (2012 Jul 3)
- Shaojing Wu, Changhong Li Influence of Maternal Fish Oil Supplementation on the Risk of Asthma or Wheeze in Children: A Meta-Analysis of Randomized Controlled Trials. *Front Pediatr*. (2022 Feb 21)
- 135. Louise M Burke, John A Hawley, Stephen H S Wong, Asker E Jeukendrup Carbohydrates for training and competition. *J Sports Sci.* (2011)
- 136. Burke LM, Ross ML, Garvican-Lewis LA, Welvaert M, Heikura IA, Forbes SG, Mirtschin JG, Cato LE, Strobel N, Sharma AP, Hawley JA Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J Physiol*. (2017 May 1)
- 137. Shian-Ling Keng, Moria J Smoski, Clive J Robins Effects of mindfulness on psychological health: a review of empirical studies. *Clin Psychol Rev.* (2011 Aug)
- 138. Dariush Mozaffarian, Emelia J Benjamin, Alan S Go, Donna K Arnett, Michael J Blaha, Mary Cushman, Sarah de Ferranti, Jean-Pierre Després, Heather J Fullerton, Virginia J Howard, Mark D Huffman, Suzanne E Judd, Brett M Kissela, Daniel T Lackland, Judith H Lichtman, Lynda D Lisabeth, Simin Liu, Rachel H Mackey, David B Matchar, Darren K McGuire, Emile R Mohler 3rd, Claudia S Moy, Paul Muntner, Michael E Mussolino, Khurram Nasir, Robert W Neumar, Graham Nichol, Latha Palaniappan, Dilip K Pandey, Mathew J Reeves, Carlos J Rodriguez, Paul D Sorlie, Joel Stein, Amytis Towfighi, Tanya N Turan, Salim S Virani, Joshua Z Willey, Daniel Woo, Robert W Yeh, Melanie B Turner, American Heart Association Statistics Committee and Stroke Statistics Subcommittee Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. (2015 Jan 27)
- 139. Marjorie L McCullough, Kati Chevaux, Lilian Jackson, Mack Preston, Gregorio Martinez, Harold H Schmitz, Caroline Coletti, Hannia Campos, Norman K Hollenberg Hypertension, the Kuna, and the epidemiology of flavanols. *J Cardiovasc Pharmacol*. (2006)
- 140. Karin Ried, Peter Fakler, Nigel P Stocks Effect of cocoa on blood pressure. Cochrane Database Syst

Rev. (2017 Apr 25)

- 141. Yongcheng Ren, Yu Liu, Xi-Zhuo Sun, Bing-Yuan Wang, Yang Zhao, De-Chen Liu, Dong-Dong Zhang, Xue-Jiao Liu, Rui-Yuan Zhang, Hao-Hang Sun, Fei-Yan Liu, Xu Chen, Cheng Cheng, Lei-Lei Liu, Qiong-Gui Zhou, Ming Zhang, Dong-Sheng Hu Chocolate consumption and risk of cardiovascular diseases: a meta-analysis of prospective studies. *Heart*. (2019 Jan)
- 142. Christian Heiss, Petra Kleinbongard, Andrè Dejam, Sandra Perré, Hagen Schroeter, Helmut Sies, Malte Kelm Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers. J Am Coll Cardiol. (2005 Oct 4)
- 143. Dirk Taubert, Renate Roesen, Clara Lehmann, Norma Jung, Edgar Schömig Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. JAMA. (2007 Jul 4)
- 144. Naomi D L Fisher, Meghan Hughes, Marie Gerhard-Herman, Norman K Hollenberg Flavanol-rich coccoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens*. (2003 Dec)
- 145. Valeria Ludovici, Jens Barthelmes, Matthias P Nägele, Frank Enseleit, Claudio Ferri, Andreas J Flammer, Frank Ruschitzka, Isabella Sudano Cocoa, Blood Pressure, and Vascular Function. Front Nutr. (2017 Aug 2)
- 146. Israel Ramirez-Sanchez, Lisandro Maya, Guillermo Ceballos, Francisco Villarreal (-)-epicatechin activation of endothelial cell endothelial nitric oxide synthase, nitric oxide, and related signaling pathways. *Hypertension*. (2010 Jun)
- 147. Israel Ramirez-Sanchez, Lisandro Maya, Guillermo Ceballos, Francisco Villarreal (-)-Epicatechin induces calcium and translocation independent eNOS activation in arterial endothelial cells. *Am J Physiol Cell Physiol*. (2011 Apr)
- 148. Tatjana Brossette, Claas Hundsdörfer, Klaus-Dietrich Kröncke, Helmut Sies, Wilhelm Stahl Direct evidence that (-)-epicatechin increases nitric oxide levels in human endothelial cells. *Eur J Nutr*. (2011 Oct)
- 149. Eloi Chazelas, Bernard Srour, Elisa Desmetz, Emmanuelle Kesse-Guyot, Chantal Julia, Valérie Deschamps, Nathalie Druesne-Pecollo, Pilar Galan, Serge Hercberg, Paule Latino-Martel, Mélanie Deschasaux, Mathilde Touvier Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort. BMJ. (2019 Jul 10)
- 150. Sharmin Hossain, May A Beydoun, Hind A Beydoun, Xiaoli Chen, Alan B Zonderman, Richard J Wood Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clin Nutr ESPEN*. (2019 Apr)
- 151. Pablo Hernández-Alonso, Hatim Boughanem, Silvia Canudas, Nerea Becerra-Tomás, María Fernández de la Puente, Nancy Babio, Manuel Macias-Gonzalez, Jordi Salas-Salvadó Circulating

vitamin D levels and colorectal cancer risk: A meta-analysis and systematic review of case-control and prospective cohort studies. *Crit Rev Food Sci Nutr*. (2021 Jul 5)

- 152. Liqun Zhang, Sihai Wang, Xiaoyu Che, Xuehui Li Vitamin D and lung cancer risk: a comprehensive review and meta-analysis. *Cell Physiol Biochem*. (2015)
- 153. Xiao-Fei Guo, Ting Zhao, Jian-Min Han, Shan Li, Duo Li Vitamin D and liver cancer risk: A metaanalysis of prospective studies. *Asia Pac J Clin Nutr*. (2020)
- 154. Christine Blume, Corrado Garbazza, Manuel Spitschan Effects of light on human circadian rhythms, sleep and mood. *Somnologie (Berl)*. (2019 Sep)
- 155. Asta Juzeniene, Johan Moan Beneficial effects of UV radiation other than via vitamin D production. *Dermatoendocrinol*. (2012 Apr 1)
- 156. Shang-Ru Tsai, Michael R Hamblin Biological effects and medical applications of infrared radiation. *J Photochem Photobiol B*. (2017 May)
- 157. Dong-Hee Koh, Ju-Hyun Park, Sang-Gil Lee, Hwan-Cheol Kim, Hyejung Jung, Inah Kim, Sangjun Choi, Donguk Park Assessment of sunlight exposure across industries and occupations using blood vitamin D as a biomarker. *J Occup Health*. (2022 Jan)
- 158. Hajar Mazahery, Pamela R von Hurst Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. *Nutrients*. (2015 Jun 25)
- 159. Béatrice Lauby-Secretan, Chiara Scoccianti, Dana Loomis, Yann Grosse, Franca Bianchini, Kurt Straif, International Agency for Research on Cancer Handbook Working Group Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med*. (2016 Aug 25)
- 160. Silva MC, Furlanetto TW Does serum 25-hydroxyvitamin D decrease during acute-phase response? A systematic review. *Nutr Res.* (2015 Feb)
- 161. Rawia A Ghashut, Dinesh Talwar, John Kinsella, Andrew Duncan, Donald C McMillan The effect of the systemic inflammatory response on plasma vitamin 25 (OH) D concentrations adjusted for albumin. *PLoS One*. (2014 Mar 25)
- 162. Ifigenia Kostoglou-Athanassiou, Eleni Pantazi, Sofoklis Kontogiannis, Dimitrios Kousouris, Iordanis Mavropoulos, Panagiotis Athanassiou Vitamin D in acutely ill patients. J Int Med Res. (2018 Oct)
- 163. Ulrike Lehmann, Hanne Rosendahl Gjessing, Frank Hirche, Andreas Mueller-Belecke, Oddrun Anita Gudbrandsen, Per Magne Ueland, Gunnar Mellgren, Lotte Lauritzen, Helen Lindqvist, Anita Lill Hansen, Arja T Erkkilä, Gerda K Pot, Gabriele I Stangl, Jutta Dierkes Efficacy of fish intake on vitamin D status: a meta-analysis of randomized controlled trials. Am J Clin Nutr. (2015 Oct)
- 164. Caroline S Stokes, Dietrich A Volmer, Frank Grünhage, Frank Lammert Vitamin D in chronic liver

disease. Liver Int. (2013 Mar)

- 165. Kim Robien, Sarah J Oppeneer, Julia A Kelly, Jill M Hamilton-Reeves Drug-vitamin D interactions: a systematic review of the literature. *Nutr Clin Pract*. (2013 Apr)
- 166. Uwe Gröber, Klaus Kisters Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol. (2012 Apr 1)
- 167. Helen A Valsamis, Surender K Arora, Barbara Labban, Samy I McFarlane Antiepileptic drugs and bone metabolism. *Nutr Metab (Lond)*. (2006 Sep 6)
- 168. Shoaib Afzal, Peter Brøndum-Jacobsen, Stig E Bojesen, Børge G Nordestgaard Genetically low vitamin D concentrations and increased mortality: Mendelian randomisation analysis in three large cohorts. *BMJ*. (2014 Nov 18)
- 169. Jue-Sheng Ong, Puya Gharahkhani, Jiyuan An, Matthew H Law, David C Whiteman, Rachel E Neale, Stuart MacGregor Vitamin D and overall cancer risk and cancer mortality: a Mendelian randomization study. *Hum Mol Genet*. (2018 Dec 15)
- 170. Rachel E Neale, Catherine Baxter, Briony Duarte Romero, Donald S A McLeod, Dallas R English, Bruce K Armstrong, Peter R Ebeling, Gunter Hartel, Michael G Kimlin, Rachel O'Connell, Jolieke C van der Pols, Alison J Venn, Penelope M Webb, David C Whiteman, Mary Waterhouse The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. Lancet Diabetes Endocrinol. (2022 Feb)
- 171. Richard B Mazess, Heike A Bischoff-Ferrari, Bess Dawson-Hughes Vitamin D: Bolus Is Bogus-A Narrative Review. JBMR Plus. (2021 Oct 30)
- 172. Jawad Fares, Mohamad Y Fares, Hussein H Khachfe, Hamza A Salhab, Youssef Fares Molecular principles of metastasis: a hallmark of cancer revisited. *Signal Transduct Target Ther*. (2020 Mar 12)
- 173. Paulette D Chandler, Wendy Y Chen, Oluremi N Ajala, Aditi Hazra, Nancy Cook, Vadim Bubes, I-Min Lee, Edward L Giovannucci, Walter Willett, Julie E Buring, JoAnn E Manson, VITAL Research Group Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. JAMA Netw Open. (2020 Nov 2)
- 174. Yongqiang Zheng, Ying Chen, Kaixu Yu, Yun Yang, Xindi Wang, Xue Yang, Jiaxin Qian, Ze-Xian Liu, Bian Wu Fatal Infections Among Cancer Patients: A Population-Based Study in the United States. Infect Dis Ther. (2021 Jun)
- 175. Hae-Eun Cho, Seung-Kwon Myung, Herim Cho Efficacy of Vitamin D Supplements in Prevention of Acute Respiratory Infection: A Meta-Analysis for Randomized Controlled Trials. *Nutrients*. (2022 Feb 15)
- 176. Hamza El Hadi, Angelo Di Vincenzo, Roberto Vettor, Marco Rossato Cardio-Metabolic Disorders in

#### Non-Alcoholic Fatty Liver Disease. Int J Mol Sci. (2019 May 6)

- 177. Margalida Monserrat-Mesquida, Magdalena Quetglas-Llabrés, Manuela Abbate, Sofía Montemayor, Catalina M Mascaró, Miguel Casares, Silvia Tejada, Itziar Abete, Maria Angeles Zulet, Josep A Tur, J Alfredo Martínez, Antoni Sureda Oxidative Stress and Pro-Inflammatory Status in Patients with Non-Alcoholic Fatty Liver Disease. Antioxidants (Basel). (2020 Aug 16)
- 178. Kris V Kowdley, Patricia Belt, Laura A Wilson, Matthew M Yeh, Brent A Neuschwander-Tetri, Naga Chalasani, Arun J Sanyal, James E Nelson, NASH Clinical Research Network Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology*. (2012 Jan)
- 179. Justine Mathieu-Denoncourt, Sarah J Wallace, Shane R de Solla, Valerie S Langlois Plasticizer endocrine disruption: Highlighting developmental and reproductive effects in mammals and nonmammalian aquatic species. *Gen Comp Endocrinol*. (2015 Aug 1)
- 180. Sarah Hatch Pollard, Kyley J Cox, Brenna E Blackburn, Diana G Wilkins, Douglas T Carrell, Joseph B Stanford, Christina A Porucznik Male exposure to bisphenol A (BPA) and semen quality in the Home Observation of Periconceptional Exposures (HOPE) cohort. *Reprod Toxicol*. (2019 Dec)
- 181. Stephanie M Matt, Jacob M Allen, Marcus A Lawson, Lucy J Mailing, Jeffrey A Woods, Rodney W Johnson Butyrate and Dietary Soluble Fiber Improve Neuroinflammation Associated With Aging in Mice. Front Immunol. (2018 Aug 14)
- 182. Strassman BI The Biology of Menstruation in Homo Sapiens: Total Lifetime Menses, Fecundity, and Nonsynchrony in a Natural-Fertility Population. *Current Anthropology*. (1997)
- 183. Martin Andersson, Mari Persson, Anette Kjellgren Psychoactive substances as a last resort-a qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduct J.* (2017 Sep 5)
- 184. Jennifer K Harrison, David J Stott, Rupert McShane, Anna H Noel-Storr, Rhiannon S Swann-Price, Terry J Quinn Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early diagnosis of dementia across a variety of healthcare settings. Cochrane Database Syst Rev. (2016 Nov 21)
- 185. Amanda M Di Battista, Nicolette M Heinsinger, G William Rebeck Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function. *Curr Alzheimer Res.* (2016)
- 186. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. (2004 May)
- 187. Antonio Ceriello, Stefano Genovese Atherogenicity of postprandial hyperglycemia and lipotoxicity. *Rev Endocr Metab Disord*. (2016 Mar)
- 188. Jenna B Gillen, Stephanie Estafanos, Alexa Govette Exercise-nutrient interactions for improved
## postprandial glycemic control and insulin sensitivity. Appl Physiol Nutr Metab. (2021 Aug)

- 189. Seth R Flaxman, Rupert R A Bourne, Serge Resnikoff, Peter Ackland, Tasanee Braithwaite, Maria V Cicinelli, Aditi Das, Jost B Jonas, Jill Keeffe, John H Kempen, Janet Leasher, Hans Limburg, Kovin Naidoo, Konrad Pesudovs, Alex Silvester, Gretchen A Stevens, Nina Tahhan, Tien Y Wong, Hugh R Taylor, Vision Loss Expert Group of the Global Burden of Disease Study Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. (2017 Dec)
- 190. Hana Kahleova, Rebecca Fleeman, Adela Hlozkova, Richard Holubkov, Neal D Barnard A plantbased diet in overweight individuals in a 16-week randomized clinical trial: metabolic benefits of plant protein. *Nutr Diabetes*. (2018 Nov 2)
- 191. Michelle McMacken, Sapana Shah A plant-based diet for the prevention and treatment of type 2 diabetes. *J Geriatr Cardiol*. (2017 May)
- 192. M F McCarty Vegan proteins may reduce risk of cancer, obesity, and cardiovascular disease by promoting increased glucagon activity. *Med Hypotheses*. (1999 Dec)
- 193. Jia Yang, Jun Yu The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. *Protein Cell*. (2018 May)
- 194. Niv Zmora, Jotham Suez, Eran Elinav You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol.* (2019 Jan)
- 195. Jane M Natividad, Bruno Lamas, Hang Phuong Pham, Marie-Laure Michel, Dominique Rainteau, Chantal Bridonneau, Gregory da Costa, Johan van Hylckama Vlieg, Bruno Sovran, Celia Chamignon, Julien Planchais, Mathias L Richard, Philippe Langella, Patrick Veiga, Harry Sokol Bilophila wadsworthia aggravates high fat diet induced metabolic dysfunctions in mice. Nat Commun. (2018 Jul 18)
- 196. Jessie Qiaoyi Liang, Tong Li, Geicho Nakatsu, Ying-Xuan Chen, Tung On Yau, Eagle Chu, Sunny Wong, Chun Ho Szeto, Siew C Ng, Francis K L Chan, Jing-Yuan Fang, Joseph J Y Sung, Jun Yu A novel faecal Lachnoclostridium marker for the non-invasive diagnosis of colorectal adenoma and cancer. *Gut*. (2020 Jul)
- 197. Spencer C Peck, Karin Denger, Anna Burrichter, Stephania M Irwin, Emily P Balskus, David Schleheck A glycyl radical enzyme enables hydrogen sulfide production by the human intestinal bacterium Bilophila wadsworthia. *Proc Natl Acad Sci U S A*. (2019 Feb 19)
- 198. Lara Jochum, Bärbel Stecher Label or Concept What Is a Pathobiont?. *Trends Microbiol*. (2020 Oct)
- 199. Messina M Soy and Health Update: Evaluation of the Clinical and Epidemiologic Literature. *Nutrients*. (2016 Nov 24)

## 200. 2020 Alzheimer's disease facts and figures. Alzheimers Dement. (2020 Mar 10)

- 201. Stephen Cunnane, Scott Nugent, Maggie Roy, Alexandre Courchesne-Loyer, Etienne Croteau, Sébastien Tremblay, Alex Castellano, Fabien Pifferi, Christian Bocti, Nancy Paquet, Hadi Begdouri, M'hamed Bentourkia, Eric Turcotte, Michèle Allard, Pascale Barberger-Gateau, Tamas Fulop, Stanley I Rapoport Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition. (2011 Jan)
- 202. Yang An, Vijay R Varma, Sudhir Varma, Ramon Casanova, Eric Dammer, Olga Pletnikova, Chee W Chia, Josephine M Egan, Luigi Ferrucci, Juan Troncoso, Allan I Levey, James Lah, Nicholas T Seyfried, Cristina Legido-Quigley, Richard O'Brien, Madhav Thambisetty Evidence for brain glucose dysregulation in Alzheimer's disease. *Alzheimers Dement*. (2018 Mar)
- 203. Alexandre Courchesne-Loyer, Etienne Croteau, Christian-Alexandre Castellano, Valérie St-Pierre, Marie Hennebelle, Stephen C Cunnane Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. J Cereb Blood Flow Metab. (2017 Jul)
- 204. Okudan N, Gokbel H The effects of creatine supplementation on performance during the repeated bouts of supramaximal exercise. *J Sports Med Phys Fitness*. (2005 Dec)
- 205. Sven J van der Lee, Charlotte E Teunissen, René Pool, Martin J Shipley, Alexander Teumer, Vincent Chouraki, Debora Melo van Lent, Juho Tynkkynen, Krista Fischer, Jussi Hernesniemi, Toomas Haller, Archana Singh-Manoux, Aswin Verhoeven, Gonneke Willemsen, Francisca A de Leeuw, Holger Wagner, Jenny van Dongen, Johannes Hertel, Kathrin Budde, Ko Willems van Dijk, Leonie Weinhold, M Arfan Ikram, Maik Pietzner, Markus Perola, Michael Wagner, Nele Friedrich, P Eline Slagboom, Philip Scheltens, Qiong Yang, Robert E Gertzen, Sarah Egert, Shuo Li, Thomas Hankemeier, Catharina E M van Beijsterveldt, Ramachandran S Vasan, Wolfgang Maier, Carel F W Peeters, Hans Jörgen Grabe, Alfredo Ramirez, Sudha Seshadri, Andres Metspalu, Mika Kivimäki, Veikko Salomaa, Ayşe Demirkan, Dorret I Boomsma, Wiesje M van der Flier, Najaf Amin, Cornelia M van Duijn Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies. *Alzheimers Dement*. (2018 Jun)
- 206. Martha Clare Morris, Denis A Evans, Julia L Bienias, Christine C Tangney, David A Bennett, Robert S Wilson, Neelum Aggarwal, Julie Schneider Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol*. (2003 Jul)
- 207. Isabelle Bauer, Matthew Hughes, Renee Rowsell, Robyn Cockerell, Andrew Pipingas, Sheila Crewther, David Crewther Omega-3 supplementation improves cognition and modifies brain activation in young adults. *Hum Psychopharmacol*. (2014 Mar)
- 208. Vanessa Danthiir, Diane E Hosking, Ted Nettelbeck, Andrew D Vincent, Carlene Wilson, Nathan O'Callaghan, Eva Calvaresi, Peter Clifton, Gary A Wittert An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively

normal older adults. Am J Clin Nutr. (2018 May 1)

- 209. Peter J Rogers, Katherine M Appleton, David Kessler, Tim J Peters, David Gunnell, Robert C Hayward, Susan V Heatherley, Leonie M Christian, Sarah A McNaughton, Andy R Ness No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *Br J Nutr*. (2008 Feb)
- 210. Welma Stonehouse, Cathryn A Conlon, John Podd, Stephen R Hill, Anne M Minihane, Crystal Haskell, David Kennedy DHA Supplementation Improved Both Memory and Reaction Time in Healthy Young Adults: A Randomized Controlled Trial. *Am J Clin Nutr*. (2013 May)
- 211. Mary N Haan, Elizabeth R Mayeda Apolipoprotein E Genotype and Cardiovascular Diseases in the Elderly. *Curr Cardiovasc Risk Rep*. (2010 Sep)
- 212. O van de Rest, J M Geleijnse, F J Kok, W A van Staveren, C Dullemeijer, M G M Olderikkert, A T F Beekman, C P G M de Groot Effect of Fish Oil on Cognitive Performance in Older Subjects: A Randomized, Controlled Trial. *Neurology*. (2008 Aug 5)
- 213. Jae Jeong Yang, Danxia Yu, Yong-Bing Xiang, William Blot, Emily White, Kim Robien, Rashmi Sinha, Yikyung Park, Yumie Takata, DeAnn Lazovich, Yu-Tang Gao, Xuehong Zhang, Qing Lan, Bas Buenode-Mesquita, Ingegerd Johansson, Rosario Tumino, Elio Riboli, Anne Tjønneland, Guri Skeie, J Ramón Quirós, Mattias Johansson, Stephanie A Smith-Warner, Wei Zheng, Xiao-Ou Shu Association of Dietary Fiber and Yogurt Consumption With Lung Cancer Risk: A Pooled Analysis. JAMA Oncol. (2020 Feb 1)
- 214. E Juulia Paavonen, Katri Räikkönen, Anu-Katriina Pesonen, Jari Lahti, Niina Komsi, Kati Heinonen, Anna-Liisa Järvenpää, Timo Strandberg, Eero Kajantie, Tarja Porkka-Heiskanen Sleep quality and cognitive performance in 8-year-old children. *Sleep Med*. (2010 Apr)
- 215. Chithambara Thanu Sivakumar, Mahalakshmi Rajan, Umapathy Pasupathy, Sathya Chidambaram, Nithya Baskar Effect of sleep habits on academic performance in schoolchildren age 6 to 12 years: a cross-sectional observation study. *J Clin Sleep Med*. (2022 Jan 1)
- 216. Yanhui Wu, Qinghai Gong, Zhuquan Zou, Hui Li, Xiaohong Zhang Short sleep duration and obesity among children: A systematic review and meta-analysis of prospective studies. *Obes Res Clin Pract.* (Mar-Apr 2017)
- 217. Jean-Philippe Chaput, Mark S Tremblay, Peter T Katzmarzyk, Mikael Fogelholm, Gang Hu, Carol Maher, Jose Maia, Timothy Olds, Vincent Onywera, Olga L Sarmiento, Martyn Standage, Catrine Tudor-Locke, Hugues Sampasa-Kanyinga, ISCOLE Research Group Sleep patterns and sugar-sweetened beverage consumption among children from around the world. *Public Health Nutr*. (2018 Sep)
- 218. Shalini Paruthi, Lee J Brooks, Carolyn D'Ambrosio, Wendy A Hall, Suresh Kotagal, Robin M Lloyd, Beth A Malow, Kiran Maski, Cynthia Nichols, Stuart F Quan, Carol L Rosen, Matthew M Troester,

Merrill S Wise Consensus Statement of the American Academy of Sleep Medicine on the Recommended Amount of Sleep for Healthy Children: Methodology and Discussion. *J Clin Sleep Med*. (2016 Nov 15)

- 219. Barbara Marlenga, Nathan King, William Pickett, Joshua Lawson, Louise Hagel, James A Dosman, Saskatchewan Farm Injury Cohort Study Team Impact of sleep on injury risk among rural children. Paediatr Child Health. (2017 Jul)
- 220. Nelina Ruiz, Airam Rangel, Carla Rodríguez, Lisette Rodríguez, Valeria Rodríguez Relationship among nocturnal sleep deficit, excess weight and metabolic alterations in adolescents. *Arch Argent Pediatr*. (2014 Dec)
- 221. Kwok-Kei Mak, So-Lun Lee, Sai-Yin Ho, Wing-Sze Lo, Tai-Hing Lam Sleep and academic performance in Hong Kong adolescents. *J Sch Health*. (2012 Nov)
- 222. Damien Leger, François Beck, Jean-Baptiste Richard, Emmanuelle Godeau Total sleep time severely drops during adolescence. *PLoS One*. (2012)
- 223. Prakash Acharya, Maya S Safarova, Tarun Dalia, Rajani Bharati, Sagar Ranka, Mohinder Vindhyal, Sania Jiwani, Rajat S Barua Effects of Vitamin D Supplementation and 25-Hydroxyvitamin D Levels on the Risk of Atrial Fibrillation. *Am J Cardiol*. (2022 Mar 31)
- 224. James P Lugo, Zainulabedin M Saiyed, Nancy E Lane Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. *Nutr J*. (2016 Jan 29)
- 225. Lugo JP, Saiyed ZM, Lau FC, Molina JP, Pakdaman MN, Shamie AN, Udani JK Undenatured type II collagen (UC-II®) for joint support: a randomized, double-blind, placebo-controlled study in healthy volunteers. *J Int Soc Sports Nutr*. (2013 Oct 24)
- 226. Cuiying Wang, Yuying Yang, Xiao Ding, Jiamin Li, Xue Zhou, Jing Teng, Xianghua Qi Efficacy and safety of Shumian capsules in treating insomnia: A systematic review and meta-analysis. *Medicine* (*Baltimore*). (2021 Dec 17)
- 227. Shunhua Li, Lu Ding, Xinhua Xiao Comparing the Efficacy and Safety of Low-Carbohydrate Diets with Low-Fat Diets for Type 2 Diabetes Mellitus Patients: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Int J Endocrinol*. (2021 Dec 6)
- 228. Zobair Younossi, Frank Tacke, Marco Arrese, Barjesh Chander Sharma, Ibrahim Mostafa, Elisabetta Bugianesi, Vincent Wai-Sun Wong, Yusuf Yilmaz, Jacob George, Jiangao Fan, Miriam B Vos Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Hepatology*. (2019 Jun)
- 229. Marno C Ryan, Catherine Itsiopoulos, Tania Thodis, Glenn Ward, Nicholas Trost, Sophie Hofferberth, Kerin O'Dea, Paul V Desmond, Nathan A Johnson, Andrew M Wilson The

Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with nonalcoholic fatty liver disease. *J Hepatol*. (2013 Jul)

- 230. Catherine Properzi, Therese A O'Sullivan, Jill L Sherriff, Helena L Ching, Garry P Jeffrey, Rachel F Buckley, Jonathan Tibballs, Gerry C MacQuillan, George Garas, Leon A Adams Ad Libitum Mediterranean and Low-Fat Diets Both Significantly Reduce Hepatic Steatosis: A Randomized Controlled Trial. *Hepatology*. (2018 Nov)
- 231. Naga Chalasani, Zobair Younossi, Joel E Lavine, Michael Charlton, Kenneth Cusi, Mary Rinella, Stephen A Harrison, Elizabeth M Brunt, Arun J Sanyal The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. (2018 Jan)
- 232. Lutgarda Bozzetto, Anna Prinster, Giovanni Annuzzi, Lucia Costagliola, Anna Mangione, Alessandra Vitelli, Raffaella Mazzarella, Margaret Longobardo, Marcello Mancini, Carlo Vigorito, Gabriele Riccardi, Angela A Rivellese Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. *Diabetes Care*. (2012 Jul)
- 233. Isabel Errazuriz, Simmi Dube, Michael Slama, Roberto Visentin, Sunita Nayar, Helen O'Connor, Claudio Cobelli, Swapan Kumar Das, Ananda Basu, Walter Karl Kremers, John Port, Rita Basu Randomized Controlled Trial of a MUFA or Fiber-Rich Diet on Hepatic Fat in Prediabetes. J Clin Endocrinol Metab. (2017 May 1)
- 234. Bjermo H, Iggman D, Kullberg J, Dahlman I, Johansson L, Persson L, Berglund J, Pulkki K, Basu S, Uusitupa M, Rudling M, Arner P, Cederholm T, Ahlström H, Risérus U Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. *Am J Clin Nutr*. (2012 May)
- 235. Rosqvist F, Iggman D, Kullberg J, Cedernaes J, Johansson HE, Larsson A, Johansson L, Ahlström H, Arner P, Dahlman I, Risérus U Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. *Diabetes*. (2014 Jul)
- 236. Fredrik Rosqvist, Joel Kullberg, Marcus Ståhlman, Jonathan Cedernaes, Kerstin Heurling, Hans-Erik Johansson, David Iggman, Helena Wilking, Anders Larsson, Olof Eriksson, Lars Johansson, Sara Straniero, Mats Rudling, Gunnar Antoni, Mark Lubberink, Marju Orho-Melander, Jan Borén, Håkan Ahlström, Ulf Risérus Overeating Saturated Fat Promotes Fatty Liver and Ceramides Compared With Polyunsaturated Fat: A Randomized Trial. J Clin Endocrinol Metab. (2019 Dec 1)
- 237. Veronika A Prikhodko, Natalia N Bezborodkina, Sergey V Okovityi Pharmacotherapy for Non-Alcoholic Fatty Liver Disease: Emerging Targets and Drug Candidates. *Biomedicines*. (2022 Jan 26)
- 238. Maria Maersk, Anita Belza, Hans Stødkilde-Jørgensen, Steffen Ringgaard, Elizaveta Chabanova, Henrik Thomsen, Steen B Pedersen, Arne Astrup, Bjørn Richelsen Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention

study. Am J Clin Nutr. (2012 Feb)

- 239. Jean-Marc Schwarz, Susan M Noworolski, Michael J Wen, Artem Dyachenko, Jessica L Prior, Melissa E Weinberg, Laurie A Herraiz, Viva W Tai, Nathalie Bergeron, Thomas P Bersot, Madhu N Rao, Morris Schambelan, Kathleen Mulligan Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. J Clin Endocrinol Metab. (2015 Jun)
- 240. Jean-Marc Schwarz, Susan M Noworolski, Ayca Erkin-Cakmak, Natalie J Korn, Michael J Wen, Viva W Tai, Grace M Jones, Sergiu P Palii, Moises Velasco-Alin, Karen Pan, Bruce W Patterson, Alejandro Gugliucci, Robert H Lustig, Kathleen Mulligan Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children With Obesity. *Gastroenterology*. (2017 Sep)
- 241. Jeffrey B Schwimmer, Patricia Ugalde-Nicalo, Jean A Welsh, Jorge E Angeles, Maria Cordero, Kathryn E Harlow, Adina Alazraki, Janis Durelle, Jack Knight-Scott, Kimberly P Newton, Rebecca Cleeton, Cynthia Knott, Juna Konomi, Michael S Middleton, Curtis Travers, Claude B Sirlin, Albert Hernandez, Ahlia Sekkarie, Courtney McCracken, Miriam B Vos Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys: A Randomized Clinical Trial. *JAMA*. (2019 Jan 22)
- 242. Catherine C Cohen, Kelvin W Li, Adina L Alazraki, Carine Beysen, Carissa A Carrier, Rebecca L Cleeton, Mohamad Dandan, Janet Figueroa, Jack Knight-Scott, Cynthia J Knott, Kimberly P Newton, Edna M Nyangau, Claude B Sirlin, Patricia A Ugalde-Nicalo, Jean A Welsh, Marc K Hellerstein, Jeffrey B Schwimmer, Miriam B Vos Dietary sugar restriction reduces hepatic de novo lipogenesis in adolescent boys with fatty liver disease. *J Clin Invest*. (2021 Dec 15)
- 243. Banafshe Khodami, Behzad Hatami, Zahra Yari, Seyyed Moayyed Alavian, Amir Sadeghi, Hamed Kord Varkaneh, Heitor O Santos, Azita Hekmatdoost Effects of a low free sugar diet on the management of nonalcoholic fatty liver disease: a randomized clinical trial. *Eur J Clin Nutr*. (2022 Jan 20)
- 244. Shira Zelber-Sagi, Federico Salomone, Liat Mlynarsky The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: Evidence and plausible mechanisms. *Liver Int*. (2017 Jul)
- 245. Erratum Regarding "KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update" (Am J Kidney Dis. 2020;763suppl 1:S1-S107). *Am J Kidney Dis*. (2021 Feb)
- 246. Juan J Carrero, Ailema González-Ortiz, Carla M Avesani, Stephan J L Bakker, Vincenzo Bellizzi, Philippe Chauveau, Catherine M Clase, Adamasco Cupisti, Angeles Espinosa-Cuevas, Pablo Molina, Karine Moreau, Giorgina B Piccoli, Adrian Post, Siren Sezer, Denis Fouque Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol*. (2020 Sep)
- 247. Kajal P Patel, Frank J-G Luo, Natalie S Plummer, Thomas H Hostetter, Timothy W Meyer The

production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. *Clin J Am Soc Nephrol.* (2012 Jun)

- 248. Liliana Garneata, Alexandra Stancu, Diana Dragomir, Gabriel Stefan, Gabriel Mircescu Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression. *J Am Soc Nephrol*. (2016 Jul)
- 249. Thomas H Inge, Meg Zeller, Carroll Harmon, Michael Helmrath, Judy Bean, Avani Modi, Mary Horlick, Maninder Kalra, Stavra Xanthakos, Rosemary Miller, Rachel Akers, Anita Courcoulas Teen-Longitudinal Assessment of Bariatric Surgery: methodological features of the first prospective multicenter study of adolescent bariatric surgery. *J Pediatr Surg*. (2007 Nov)
- 250. Hendrik Vilstrup, Piero Amodio, Jasmohan Bajaj, Juan Cordoba, Peter Ferenci, Kevin D Mullen, Karin Weissenborn, Philip Wong Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. (2014 Aug)
- 251. Booth SL Vitamin K: food composition and dietary intakes. Food Nutr Res. (2012)
- 252. J Graff, K Brinch, J L Madsen Gastrointestinal mean transit times in young and middle-aged healthy subjects. *Clin Physiol*. (2001 Mar)
- 253. Anjani Chandra, Casey E Copen, Elizabeth Hervey Stephen Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. *Natl Health Stat Report*. (2013 Aug 14)
- 254. Emad Babakhanzadeh, Majid Nazari, Sina Ghasemifar, Ali Khodadadian Some of the Factors Involved in Male Infertility: A Prospective Review. Int J Gen Med. (2020 Feb 5)
- 255. Rachel Busuttil Leaver Male infertility: an overview of causes and treatment options. *Br J Nurs*. (2016 Oct 13)
- 256. Stellingwerff T, Cox GR Systematic review: Carbohydrate supplementation on exercise performance or capacity of varying durations. *Appl Physiol Nutr Metab*. (2014 Sep)
- 257. Cihan Kabukçu, Nazlı Çil, Tahir Turan, Yusuf Özlülerden, Ümit Çabuş, Gülçin Abban Mete Do seasonal variations in ambient temperature, humidity and daylight duration affect semen parameters? A retrospective analysis over eight years. *Andrologia*. (2020 Nov)
- 258. Eliahu Levitas, Eitan Lunenfeld, Noemi Weisz, Michael Friger, Iris Har-Vardi Seasonal variations of human sperm cells among 6455 semen samples: a plausible explanation of a seasonal birth pattern. *Am J Obstet Gynecol*. (2013 May)
- 259. Huan Mao, Lei Feng, Wan-Xi Yang Environmental factors contributed to circannual rhythm of semen quality. *Chronobiol Int*. (2017)

- 260. Scott K Powers, W Bradley Nelson, Matthew B Hudson Exercise-induced oxidative stress in humans: cause and consequences. *Free Radic Biol Med*. (2011 Sep 1)
- 261. Artur L Bessa, Vanessa N Oliveira, Guilherme G Agostini, Renato J S Oliveira, Ana C S Oliveira, Gillian E White, Greg D Wells, David N S Teixeira, Foued S Espindola Exercise Intensity and Recovery: Biomarkers of Injury, Inflammation, and Oxidative Stress. J Strength Cond Res. (2016 Feb)
- 262. Elżbieta Poniedziałek-Czajkowska, Radzisław Mierzyński Could Vitamin D Be Effective in Prevention of Preeclampsia?. *Nutrients*. (2021 Oct 28)
- 263. Stefan Pilz, Andreas Tomaschitz, Eberhard Ritz, Thomas R Pieber Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol*. (2009 Oct)
- 264. Sunil J Wimalawansa Vitamin D and cardiovascular diseases: Causality. J Steroid Biochem Mol Biol. (2018 Jan)
- 265. Sepideh Aminzadeh-Gohari, René Günther Feichtinger, Silvia Vidali, Felix Locker, Tricia Rutherford, Maura O'Donnel, Andrea Stöger-Kleiber, Johannes Adalbert Mayr, Wolfgang Sperl, Barbara Kofler A ketogenic diet supplemented with medium-chain triglycerides enhances the anti-tumor and anti-angiogenic efficacy of chemotherapy on neuroblastoma xenografts in a CD1-nu mouse model. Oncotarget. (2017 Aug 8)
- 266. Mohammed G Abdelwahab, Kathryn E Fenton, Mark C Preul, Jong M Rho, Andrew Lynch, Phillip Stafford, Adrienne C Scheck The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma. *PLoS One*. (2012)
- 267. Johannes Rieger, Oliver Bähr, Gabriele D Maurer, Elke Hattingen, Kea Franz, Daniel Brucker, Stefan Walenta, Ulrike Kämmerer, Johannes F Coy, Michael Weller, Joachim P Steinbach ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. *Int J Oncol*. (2014 Jun)
- 268. Isabella Wy Mak, Nathan Evaniew, Michelle Ghert Lost in translation: animal models and clinical trials in cancer treatment. *Am J Transl Res.* (2014 Jan 15)
- 269. Tobias Walbert, Tom Mikkelsen Recurrent high-grade glioma: a diagnostic and therapeutic challenge. *Expert Rev Neurother*. (2011 Apr)
- 270. Lana Seguias, Katy Tapper The effect of mindful eating on subsequent intake of a high calorie snack. *Appetite*. (2018 Feb 1)
- 271. Eric Robinson, Inge Kersbergen, Suzanne Higgs Eating 'attentively' reduces later energy consumption in overweight and obese females. *Br J Nutr*. (2014 Aug 28)
- 272. Katy Tapper, Lana Seguias The effects of mindful eating on food consumption over a half-day period. *Appetite*. (2020 Feb 1)

- 273. Victoria Whitelock, Alexandra Gaglione, Jennifer Davies-Owen, Eric Robinson Focused attention during eating enhanced memory for meal satiety but did not reduce later snack intake in men: A randomised within-subjects laboratory experiment. *Appetite*. (2019 May 1)
- 274. Ju Sun Heo, Young Min Ahn, Ai-Rhan Ellen Kim, Son Moon Shin, Korean Society of Breastfeeding Medicine Breastfeeding and vitamin D. *Clin Exp Pediatr*. (2021 Dec 14)
- 275. Carol L Wagner, Thomas C Hulsey, Deanna Fanning, Myla Ebeling, Bruce W Hollis High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med*. (Summer 2006)
- 276. Sara S Oberhelman, Michael E Meekins, Philip R Fischer, Bernard R Lee, Ravinder J Singh, Stephen S Cha, Brian M Gardner, John M Pettifor, Ivana T Croghan, Tom D Thacher Maternal vitamin D supplementation to improve the vitamin D status of breast-fed infants: a randomized controlled trial. *Mayo Clin Proc.* (2013 Dec)
- 277. E E Blaak, J-M Antoine, D Benton, I Björck, L Bozzetto, F Brouns, M Diamant, L Dye, T Hulshof, J J
  Holst, D J Lamport, M Laville, C L Lawton, A Meheust, A Nilson, S Normand, A A Rivellese, S Theis,
  S S Torekov, S Vinoy Impact of Postprandial Glycaemia on Health and Prevention of Disease. Obes
  Rev. (2012 Oct)
- 278. Hanan S El-Abhar, Mona F Schaalan Phytotherapy in diabetes: Review on potential mechanistic perspectives. *World J Diabetes*. (2014 Apr 15)
- 279. Ji Hyeon Ryu, Dawon Kang Physicochemical Properties, Biological Activity, Health Benefits, and General Limitations of Aged Black Garlic: A Review. *Molecules*. (2017 Jun 1)
- 280. Ana L Colín-González, Ricardo A Santana, Carlos A Silva-Islas, Maria E Chánez-Cárdenas, Abel Santamaría, Perla D Maldonado The antioxidant mechanisms underlying the aged garlic extractand S-allylcysteine-induced protection. *Oxid Med Cell Longev*. (2012)
- 281. Sara Amor, Daniel González-Hedström, Beatriz Martín-Carro, Antonio Manuel Inarejos-García, Paula Almodóvar, Marin Prodanov, Angel Luis García-Villalón, Miriam Granado Beneficial Effects of an Aged Black Garlic Extract in the Metabolic and Vascular Alterations Induced by a High Fat/ Sucrose Diet in Male Rats. *Nutrients*. (2019 Jan 12)
- 282. Gwan Gyu Song, Sang-Cheol Bae, Young Ho Lee Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. *Clin Rheumatol*. (2012 Dec)
- 283. S Schürmann, M Kersting, U Alexy Vegetarian diets in children: a systematic review. *Eur J Nutr*. (2017 Aug)
- 284. Manfred Lamprecht, Simon Bogner, Gert Schippinger, Kurt Steinbauer, Florian Fankhauser, Seth Hallstroem, Burkhard Schuetz, Joachim F Greilberger Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded,

placebo-controlled trial. J Int Soc Sports Nutr. (2012 Sep 20)

- 285. Jamie N Pugh, Anton J M Wagenmakers, Dominic A Doran, Simon C Fleming, Barbara A Fielding, James P Morton, Graeme L Close Probiotic supplementation increases carbohydrate metabolism in trained male cyclists: a randomized, double-blind, placebo-controlled crossover trial. *Am J Physiol Endocrinol Metab*. (2020 Apr 1)
- 286. Jennifer D Parker, Makram Talih, Donald J Malec, Vladislav Beresovsky, Margaret Carroll, Joe F Gonzalez, Brady E Hamilton, Deborah D Ingram, Kenneth Kochanek, Frances McCarty, Chris Moriarity, Iris Shimizu, Alexander Strashny, Brian W Ward National Center for Health Statistics Data Presentation Standards for Proportions. Vital Health Stat 2. (2017 Aug)
- 287. Serena Tonstad, Terry Butler, Ru Yan, Gary E Fraser Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. *Diabetes Care*. (2009 May)
- 288. S Tonstad, K Stewart, K Oda, M Batech, R P Herring, G E Fraser Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. *Nutr Metab Cardiovasc Dis*. (2013 Apr)
- 289. Jocelyne R Benatar, Ralph A H Stewart Cardiometabolic risk factors in vegans; A meta-analysis of observational studies. *PLoS One*. (2018 Dec 20)
- 290. Jeenan Kaiser, Kim R van Daalen, Arjun Thayyil, Mafalda Tasso de Almeida Ribeiro Reis Cocco, Daniela Caputo, Clare Oliver-Williams A Systematic Review of the Association Between Vegan Diets and Risk of Cardiovascular Disease. J Nutr. (2021 Apr 8)
- 291. Julie A Schmidt, Sabina Rinaldi, Pietro Ferrari, Marion Carayol, David Achaintre, Augustin Scalbert, Amanda J Cross, Marc J Gunter, Georgina K Fensom, Paul N Appleby, Timothy J Key, Ruth C Travis Metabolic profiles of male meat eaters, fish eaters, vegetarians, and vegans from the EPIC-Oxford cohort. *Am J Clin Nutr*. (2015 Dec)
- 292. HAPO Study Cooperative Research Group, Boyd E Metzger, Lynn P Lowe, Alan R Dyer, Elisabeth R Trimble, Udom Chaovarindr, Donald R Coustan, David R Hadden, David R McCance, Moshe Hod, Harold David McIntyre, Jeremy J N Oats, Bengt Persson, Michael S Rogers, David A Sacks Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. (2008 May 8)
- 293. Amerigo Vitagliano, Gabriele Saccone, Erich Cosmi, Silvia Visentin, Francesco Dessole, Guido Ambrosini, Vincenzo Berghella Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Arch Gynecol Obstet*. (2019 Jan)
- 294. Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. (2020 Aug 8)

- 295. S V Bădescu, C Tătaru, L Kobylinska, E L Georgescu, D M Zahiu, A M Zăgrean, L Zăgrean The association between Diabetes mellitus and Depression. *J Med Life*. (Apr-Jun 2016)
- 296. An Pan, Michel Lucas, Qi Sun, Rob M van Dam, Oscar H Franco, Walter C Willett, JoAnn E Manson, Kathryn M Rexrode, Alberto Ascherio, Frank B Hu Increased mortality risk in women with depression and diabetes mellitus. *Arch Gen Psychiatry*. (2011 Jan)
- 297. Thomas P Blackburn Depressive disorders: Treatment failures and poor prognosis over the last 50 years. *Pharmacol Res Perspect*. (2019 May 3)
- 298. L Cinnamon Bidwell, F Joseph McClernon, Scott H Kollins Cognitive enhancers for the treatment of ADHD. *Pharmacol Biochem Behav*. (2011 Aug)
- 299. Stephen V Faraone The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev.* (2018 Apr)
- 300. Sabrina Wagner, Ravikumar Manickam, Marco Brotto, Srinivas M Tipparaju NAD + centric mechanisms and molecular determinants of skeletal muscle disease and aging. *Mol Cell Biochem*. (2022 Mar 25)
- 301. Mario Romani, Dina Carina Hofer, Elena Katsyuba, Johan Auwerx Niacin: an old lipid drug in a new NAD + dress. *J Lipid Res.* (2019 Apr)
- 302. Akbar Aliasgharzadeh, Parvin Dehghan, Bahram Pourghassem Gargari, Mohammad Asghari-Jafarabadi Resistant dextrin, as a prebiotic, improves insulin resistance and inflammation in women with type 2 diabetes: a randomised controlled clinical trial. *Br J Nutr*. (2015 Jan 28)
- 303. Willoughby DS, Boucher T, Reid J, Skelton G, Clark M Effects of 7 days of arginine-alphaketoglutarate supplementation on blood flow, plasma L-arginine, nitric oxide metabolites, and asymmetric dimethyl arginine after resistance exercise. *Int J Sport Nutr Exerc Metab*. (2011 Aug)
- 304. Liu TH, Wu CL, Chiang CW, Lo YW, Tseng HF, Chang CK No effect of short-term arginine supplementation on nitric oxide production, metabolism and performance in intermittent exercise in athletes. *J Nutr Biochem*. (2009 Jun)
- 305. Alvares TS, Conte-Junior CA, Silva JT, Paschoalin VM Acute L-Arginine supplementation does not increase nitric oxide production in healthy subjects. *Nutr Metab (Lond)*. (2012 Jun 12)
- 306. Aitor Viribay, José Burgos, Julen Fernández-Landa, Jesús Seco-Calvo, Juan Mielgo-Ayuso Effects of Arginine Supplementation on Athletic Performance Based on Energy Metabolism: A Systematic Review and Meta-Analysis. *Nutrients*. (2020 May 2)
- 307. Abel T, Knechtle B, Perret C, Eser P, von Arx P, Knecht H Influence of chronic supplementation of arginine aspartate in endurance athletes on performance and substrate metabolism a randomized, double-blind, placebo-controlled study. *Int J Sports Med*. (2005 Jun)

- 308. Thiago Silveira Alvares, Carlos Adam Conte-Junior, Joab Trajano Silva, Vânia Margaret Flosi Paschoalin L-arginine does not improve biochemical and hormonal response in trained runners after 4 weeks of supplementation. *Nutr Res.* (2014 Jan)
- 309. Clayton L Camic, Terry J Housh, Jorge M Zuniga, Russell C Hendrix, Michelle Mielke, Glen O Johnson, Richard J Schmidt Effects of arginine-based supplements on the physical working capacity at the fatigue threshold. *J Strength Cond Res.* (2010 May)
- 310. N Pahlavani, M H Entezari, M Nasiri, A Miri, M Rezaie, M Bagheri-Bidakhavidi, O Sadeghi The effect of l-arginine supplementation on body composition and performance in male athletes: a doubleblinded randomized clinical trial. *Eur J Clin Nutr*. (2017 Apr)
- 311. Nada Elbuluk, Pearl Grimes, Anna Chien, Iltefat Hamzavi, Andrew Alexis, Susan Taylor, Noelani Gonzalez, Jonathan Weiss, Seemal R Desai, Sewon Kang The Pathogenesis and Management of Acne-Induced Post-inflammatory Hyperpigmentation. *Am J Clin Dermatol*. (2021 Nov)
- 312. Qingyang Shi, Lizi Tan, Zhe Chen, Long Ge, Xiaoyan Zhang, Fengwen Yang, Chunxiang Liu, Junhua Zhang Comparative Efficacy of Pharmacological and Nonpharmacological Interventions for Acne Vulgaris: A Network Meta-Analysis. *Front Pharmacol*. (2020 Nov 26)
- 313. Esther E Fröhlich, Aitak Farzi, Raphaela Mayerhofer, Florian Reichmann, Angela Jačan, Bernhard Wagner, Erwin Zinser, Natalie Bordag, Christoph Magnes, Eleonore Fröhlich, Karl Kashofer, Gregor Gorkiewicz, Peter Holzer Cognitive impairment by antibiotic-induced gut dysbiosis: Analysis of gut microbiota-brain communication. *Brain Behav Immun*. (2016 Aug)
- 314. Mira Katan, Yeseon Park Moon, Myunghee Cho Paik, Ralph L Sacco, Clinton B Wright, Mitchell S V Elkind Infectious burden and cognitive function: the Northern Manhattan Study. Neurology. (2013 Mar 26)
- 315. GBD 2019 Diseases and Injuries Collaborators Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020 Oct 17)
- 316. Jeremy A Beard, Allison Bearden, Rob Striker Vitamin D and the anti-viral state. *J Clin Virol*. (2011 Mar)
- 317. Thomaz F S Bastiaanssen, Sofia Cussotto, Marcus J Claesson, Gerard Clarke, Timothy G Dinan, John F Cryan Gutted! Unraveling the Role of the Microbiome in Major Depressive Disorder. Harv Rev Psychiatry. (Jan/Feb 2020)
- 318. Limin Chao, Cui Liu, Senawin Sutthawongwadee, Yuefei Li, Weijie Lv, Wenqian Chen, Linzeng Yu, Jiahao Zhou, Ao Guo, Zengquan Li, Shining Guo Effects of Probiotics on Depressive or Anxiety Variables in Healthy Participants Under Stress Conditions or With a Depressive or Anxiety Diagnosis: A Meta-Analysis of Randomized Controlled Trials. Front Neurol. (2020 May 22)

- 319. Vidhi Desai, Anita L Kozyrskyj, Stuart Lau, Omolara Sanni, Liz Dennett, Jens Walter, Maria B Ospina Effectiveness of Probiotic, Prebiotic, and Synbiotic Supplementation to Improve Perinatal Mental Health in Mothers: A Systematic Review and Meta-Analysis. *Front Psychiatry*. (2021 Apr 22)
- 320. Kah Kheng Goh, Yen-Wenn Liu, Po-Hsiu Kuo, Yu-Chu Ella Chung, Mong-Liang Lu, Chun-Hsin Chen Effect of probiotics on depressive symptoms: A meta-analysis of human studies. *Psychiatry Res.* (2019 Dec)
- 321. Ruixue Huang, Ke Wang, Jianan Hu Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients*. (2016 Aug 6)
- 322. Richard T Liu, Rachel F L Walsh, Ana E Sheehan Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. *Neurosci Biobehav Rev.* (2019 Jul)
- 323. Ng QX, Peters C, Ho CYX, Lim DY, Yeo WS A meta-analysis of the use of probiotics to alleviate depressive symptoms. *J Affect Disord*. (2018 Mar 1)
- 324. Viktoriya Nikolova, Syed Yawar Zaidi, Allan H Young, Anthony J Cleare, James M Stone Gut feeling: randomized controlled trials of probiotics for the treatment of clinical depression: Systematic review and meta-analysis. *Ther Adv Psychopharmacol*. (2019 Jun 26)
- 325. Viktoriya L Nikolova, Anthony J Cleare, Allan H Young, James M Stone Updated Review and Meta-Analysis of Probiotics for the Treatment of Clinical Depression: Adjunctive vs. Stand-Alone Treatment. J Clin Med. (2021 Feb 8)
- 326. Kenji Sanada, Shinichiro Nakajima, Shunya Kurokawa, Alberto Barceló-Soler, Daisuke Ikuse, Akihito Hirata, Akira Yoshizawa, Yoshihiro Tomizawa, Montserrat Salas-Valero, Yoshihiro Noda, Masaru Mimura, Akira Iwanami, Taishiro Kishimoto Gut microbiota and major depressive disorder: A systematic review and meta-analysis. J Affect Disord. (2020 Apr 1)
- 327. Elaheh Amirani, Alireza Milajerdi, Hamed Mirzaei, Hamidreza Jamilian, Mohammad Ali Mansournia, Jamal Hallajzadeh, Amir Ghaderi The Effects of Probiotic Supplementation on Mental Health, Biomarkers of Inflammation and Oxidative Stress in Patients With Psychiatric Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Complement Ther Med*. (2020 Mar)
- 328. Violaine Mongeau-Pérusse, Suzanne Brissette, Julie Bruneau, Patricia Conrod, Simon Dubreucq, Guillaume Gazil, Emmanuel Stip, Didier Jutras-Aswad Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *Addiction*. (2021 Sep)
- 329. Chun Shing Kwok, Saadia Umar, Phyo K Myint, Mamas A Mamas, Yoon K Loke Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and metaanalysis. *Int J Cardiol*. (2014 Oct 20)

- 330. Donald M Lloyd-Jones, Yuling Hong, Darwin Labarthe, Dariush Mozaffarian, Lawrence J Appel, Linda Van Horn, Kurt Greenlund, Stephen Daniels, Graham Nichol, Gordon F Tomaselli, Donna K Arnett, Gregg C Fonarow, P Michael Ho, Michael S Lauer, Frederick A Masoudi, Rose Marie Robertson, Véronique Roger, Lee H Schwamm, Paul Sorlie, Clyde W Yancy, Wayne D Rosamond, American Heart Association Strategic Planning Task Force and Statistics Committee Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. (2010 Feb 2)
- 331. Cyrus Cooper, Nicholas C Harvey, Nicholas J Bishop, Stephen Kennedy, Aris T Papageorghiou, Inez Schoenmakers, Robert Fraser, Saurabh V Gandhi, Andrew Carr, Stefania D'Angelo, Sarah R Crozier, Rebecca J Moon, Nigel K Arden, Elaine M Dennison, Keith M Godfrey, Hazel M Inskip, Ann Prentice, M Zulf Mughal, Richard Eastell, David M Reid, M Kassim Javaid, MAVIDOS Study Group Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diabetes Endocrinol. (2016 May)
- 332. W R Kim, J R Lake, J M Smith, D P Schladt, M A Skeans, S M Noreen, A M Robinson, E Miller, J J Snyder, A K Israni, B L Kasiske OPTN/SRTR 2017 Annual Data Report: Liver. Am J Transplant. (2019 Feb)
- 333. Susan A Elmore, Eleanor H Weston Predatory Journals: What They Are and How to Avoid Them. *Toxicol Pathol.* (2020 Jun)
- 334. Chaoqiang Jiang, G Neil Thomas, Tai Hing Lam, C Mary Schooling, Weisen Zhang, Xiangqian Lao, Peymane Adab, Bin Liu, Gabriel M Leung, Kar Keung Cheng Cohort profile: The Guangzhou Biobank Cohort Study, a Guangzhou-Hong Kong-Birmingham collaboration. Int J Epidemiol. (2006 Aug)
- 335. EFSA Panel on Dietetic Products, Nutrition and Allergies (EFSA NDA Panel), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Henk Van Loveren, Marco Vinceti, Peter Willatts, Mary Fewtrell, Christel Lamberg-Allardt, Hildegard Przyrembel, Davide Arcella, Céline Dumas, Lucia Fabiani, Laura Martino, Daniela Tomcikova, Monika Neuhäuser-Berthold Update of the tolerable upper intake level for vitamin D for infants. *EFSA J.* (2018 Aug 7)
- 336. Azusa Nishino, Kazuhisa Sugimoto, Haruyo Sambe, Takashi Ichihara, Takeshi Takaha, Takashi Kuriki Effects of Dietary Paprika Xanthophylls on Ultraviolet Light-Induced Skin Damage: A Double-Blind Placebo-Controlled Study. *J Oleo Sci*. (2018 Jul 1)
- 337. Petrofsky et al pilot study: physiological evidence that heat reduces pain and muscle damage in delayed-onset muscle soreness. *clinical practice*. (2012-11)

- 338. François Bieuzen, Chris M Bleakley, Joseph Thomas Costello Contrast water therapy and exercise induced muscle damage: a systematic review and meta-analysis. *PLoS One*. (2013 Apr 23)
- 339. Jerrold S Petrofsky, Iman Akef Khowailed, Haneul Lee, Lee Berk, Gurinder S Bains, Siddhesh Akerkar, Jinal Shah, Fuad Al-Dabbak, Mike S Laymon Cold Vs. Heat After Exercise-Is There a Clear Winner for Muscle Soreness. J Strength Cond Res. (2015 Nov)
- 340. Randi Eidsmo Reinertsen, Hilde Faerevik, Kristine Holbø, Ragnhild Nesbakken, Jarl Reitan, Arne Røyset, Maria Suong Le Thi Optimizing the performance of phase-change materials in personal protective clothing systems. *Int J Occup Saf Ergon*. (2008)
- 341. Robert J Gatchel, Kathryn H Rollings Evidence-informed management of chronic low back pain with cognitive behavioral therapy. *Spine J*. (Jan-Feb 2008)