



THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY
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ABOUT CLIFF



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Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on the use of medium-chain triglycerides to mitigate 'keto-flu' and encourage faster induction of nutritional ketosis.

His doctoral thesis continued to investigate keto-flu and ketogenesis, and the effects of different types of low-carbohydrate diets along with the individualisation of dietary prescription and how 'carbohydrate tolerance' varies from person-to-person.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books, including *The Carbohydrate Appropriate Diet*, *Carb-Appropriate 101*, *Time Rich Cash Optional* and *The Credo*.

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HOW TO OPTIMISE BRAIN HEALTH & REDUCE THE RISK OF AGE-RELATIVE COGNITIVE DECLINE

Key Findings:

- A broad range of factors influence brain-health and cognitive decline
- Stress and lack of sleep and exercise are likely to worsen cognitive decline
- Quality nutrition for unprocessed foods is likely to be preventative for cognitive decline
- Ketogenic diets offer a potential preventative and treatment option for neurodegeneration
- Caffeine-containing natural beverages (coffee, tea, cacao) are neuroprotective and improve cognition
- Many herbs and supplements, including multivitamin/mineral, Brahmi, sage and related herbs might protect the brain.

In my clinical practise, we periodically survey our clients on the health conditions or outcomes that most concern them. In the early years, we would consistently hear that the biggest concern was quite simply, weight... Now though, weight and body fat have fallen behind brain health and day-to-day energy as the major concerns for our clients. This is unsurprising given the rising incidence of neurodegenerative conditions Alzheimer's, Parkinson's, and other diseases that affect the brain and central nervous system.



What are 'neurodegenerative disorders'?

Neurodegeneration is the progressive damage and destruction of neurons (brain and nervous systems cells) and/or components of those cells. This breakdown of cells results in age-related cognitive decline and in more serious cases the common neurodegenerative disorders; dementias such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (known as Lou Gehrig's disease) and Huntington's disease. According to Alzheimer's Disease International, *someone in the world develops dementia every 3 seconds*. Additionally, over 50 million people now live with dementia worldwide and this number is expected to double every 20 years.ⁱ The neurodegenerative disorders cause progressive disability, incurring a loss of cognition, memory, and physical function. Survival times are also typically short—for example, the average survival time post-diagnosis for Alzheimer's disease is only 3-9 years.

Someone in the world develops dementia every 3 seconds

What causes cognitive decline?

Neurodegenerative disorders and age-related cognitive decline are both inherited (genetic) and also result from diet and lifestyle factors. These causes include head injuries, pesticide exposure (Parkinson's), hypertension, lack of sleep, and a poor diet, along with additional risk factors of metabolic syndrome and diabetes, depression, excessive alcohol use, and tobacco use.¹

How can I improve my brain health and reduce my risk of cognitive decline?

Exercise the brain and the body
Lifestyle factors can reduce your risk of cognitive decline and even improve cognitive function. These include engaging in leisure and physical activities, playing a sport, listening to music, and doing brain-taxing activities (such as crosswords).^{1,2}

Lifestyle factors can reduce your risk of cognitive decline

People who regularly and actively participate in a variety of social, cultural, and intellectual activities that challenge them,

ⁱ <https://www.alz.co.uk/research/statistics>



experience lesser cognitive decline, perform better on cognitive tests, and are less likely to develop neurodegenerative disorders.³ Physical activity shows a consistent, yet not always significant effect on cognitive decline and dementia,^{4,6} and it's likely that the effects of physical activity alone on cognitive decline are limited, and that the best effects come from a combination of physical activity, improved diet, and regularly challenging the brain with new activities.^{5,6}

The best effects come from a combination of physical activity, improved diet, and regularly challenging the brain with new activities

Get enough sleep

Not sleeping enough, or poor sleep (i.e. insomnia, and lack of REM sleep) is a risk factor for cognitive decline and dementia.^{7,8} It is recommended that people get between 7 and 9 hours of high-quality sleep per night.

Eat a healthy diet based on natural, unrefined foods

There is a relationship between diet and cognitive decline and it's likely that eating a diet (such as the Mediterranean diet²) based mostly on natural, unrefined foods will reduce the risk of cognitive decline and

dementia. In a review of studies, it was shown that following a Mediterranean diet was associated with up to a 48% reduced risk of dementia, and those with pre-existing Alzheimer's disease had a 73% lower mortality risk than those who did not adhere to the diet.⁹

Increased fruits and vegetables

Increased intakes of fruit and vegetables are associated with both a lower risk of dementia and slowing rates of age-related cognitive decline.^{1, 10} However, subtype analysis has demonstrated that this effect is restricted to vegetables (and not fruit), with the strongest effects from cruciferous (like cabbage and broccoli) and green leafy vegetables.¹⁰ It has been further suggested that a minimum of 3 servings of vegetables should be consumed daily for this effect.¹⁰

The protective effect of fruits and vegetables is actually limited to vegetables...

Vitamin C

Maintaining healthy levels of vitamin C from nutrient-rich foods to avoid a deficiency (rather than mega-dosing) is also likely to have a protective function against age-related cognitive decline.¹¹

Omega 3 fats

The omega 3 fats EPA and especially DHA, play an important role in brain development and healthy functioning of the brain and



central nervous system.¹² Omega-3 fats are linked to reduced mental fatigue,¹³ improved memory and cognition and reduced cognitive decline,^{1, 14, 15} reduced rates of depression and improved structural integrity of the brain.^{16, 17} Plausible mechanisms also exist to suggest a protective role for fish oil in neurodegeneration in Parkinson's disease.¹⁸

Coffee and tea

Caffeine is a well-known cognitive enhancer. Evidence shows that caffeine improves attention, vigilance, reaction times, and problem-solving (especially in sleep-deprived people),^{19, 20} and improved mood and reduced fatigue even at low doses of caffeine-containing beverages (~ 1 cup of tea or coffee per day).^{20, 21}

Caffeine improves mood and reduces fatigue, even at low doses

In addition to its acute effect on mood and cognition, caffeine-containing beverages may be protective against cognitive decline and dementia,²² and coffee and tea are also associated with a reduced incidence of Parkinson's disease.^{23, 24}

Multivitamin/Multimineral

Many people do not consume sufficient essential and secondary nutrients from diet alone.^{25, 26} Multinutrient supplements are suggested to help make up for this nutrient shortfall and have resulted in improved

cognitive and memory performance in trials and reduced stress and anxiety.^{27, 28} It is likely that supporting the nutrient-sufficiency of the diet could improve long-term brain health and reduce cognitive decline.

Medium-chain triglycerides

Medium-chain triglycerides (MCT) are naturally occurring fats found in small amounts in dairy products and greater amounts in coconut oil. They are also commonly used as isolated supplement oils. MCT supplemented diets improve mental performance in those with Alzheimer's Disease and age-related cognitive decline,^{29, 30} and a single dose of 20 g MCT has been shown to improve cognition.³¹

Lion's Mane mushroom

Lion's mane (*Hericium erinaceus*) is an edible and medicinal mushroom native to North America, Europe and Asia belonging to the tooth fungus group. Lion's Mane has been shown to increase 'Nerve Growth Factor',³² which helps nerves and brain cells to grow and repair.³³⁻³⁸ Because of this brain-repair effect, Lion's Mane is being considered as one of the most promising preventatives for dementia and cognitive decline.^{39, 40} It's also been demonstrated to significantly reduce depression and anxiety,³⁴ and to improve cognitive function.⁴¹



Other supplements indicated for cognitive decline

- **Citicoline** (an intermediate in the creation of phosphatidylcholine from choline) is likely to improve cognition in both dementia patients and healthy people.⁴²
- **Acetyl-L-carnitine** has been shown to reduce fatigue, anxiety and depression, and age-related cognitive defects.⁴²
- The traditional ayurvedic herb **Brahmi** (*Bacopa monnieri*) is likely to improve cognition, memory, and reaction times.⁴³⁻⁴⁵
- The use of **Ginkgo** is controversial but recent reviews suggest a plausible role for ginkgo extracts to reduce cognitive decline (especially for patients with neuropsychiatric symptoms).⁴⁶
- **Sage** (*Salvia officinalis*) improves mood, alertness and attention, calmness, and overall cognition,⁴⁷⁻⁵⁰ and is likely to improve brain health and reduce cognitive decline.
- **Spearmint** (*Mentha spicata*) is another common herb with purported cognitive effects. Spearmint extracts have resulted in improved cognitive scores in several studies.⁵¹ (Interestingly, one of the purported 'active' chemicals,

rosmarinic acid, is also common in other herbs such as rosemary, for which it is named, and thyme).

Can a Keto diet improve cognition and prevent cognitive decline?

Ketogenic diets are low enough in carbohydrate and high enough in fat to encourage the creation of ketone bodies in higher than normal amounts (the body always produces a small amount of the ketone bodies). This ketonaemia (the presence of ketones in the blood) is called *nutritional ketosis*, which is typically just called *ketosis*. Very low carbohydrate ketogenic diets typically result in BOHB levels of ≥ 0.5 mmol/L,⁵² and this level is used as the threshold for achieving ketosis by nutrition researchers.⁵³⁻⁵⁷

A ketogenic diet is simply a diet very low in carbohydrate, low-to-high in protein, and high in fat

Ketone Bodies

The ketone bodies are 'brain-friendly' fuels derived from fatty acids and some amino acids, especially leucine and lysine (which can only be converted to ketones, not to glucose). The ketone bodies are acetoacetate, β -hydroxybutyric acid (BOHB) and acetone. While acetoacetate is the



primary ketone body, BOHB functions as the main fuel ketone.ⁱⁱ

Ketogenic Diets, Ketosis and the Brain

The potential role of ketogenic diets for brain health has been hinted for over a century and keto-diets have been used to successfully treat childhood epilepsy since the 1920s.⁵⁸⁻⁶¹ It is now known that high carbohydrate diets play a role in the causation of Alzheimer's Disease and cognitive decline, and ketogenic diets offer a potential treatment option.⁶² Both calorie-restricted diets and ketogenic diets are broadly neuroprotective,⁶³ probably due to reduced carbohydrate intake (i.e. reduced glucose-related damage to neurons) and due to the elevation of ketones and resultant reductions in oxidation and inflammation, reduced neuronal hyperexcitability, neuroprotection and neurogenesis, and improved fuel efficiency in the brain.⁶⁴

In pilot studies, elevated ketones improve memory in adults with Alzheimer's and reviews of the evidence show a positive role for the keto-diet in its treatment. Early research also suggests that keto can reduce Parkinson's disease activity.^{65, 66}

Animal studies show benefits for reducing the plaque deposits that are part of the damage inflicted by Alzheimer's,⁶⁷ along with improvements in motor function and

improved neuronal fuelling.^{68, 69} In human studies the keto-diet has been easily tolerated by Alzheimer's patients while improving cognition and memory performance vs a higher-carbohydrate control group.^{70, 71}

Ketogenic diets also reduce inflammatory damage in Parkinson's disease.⁷² In rat models, a ketogenic diet protects dopamine-producing neurons of the substantia nigra. These neurons are cells damaged by endotoxicity in Parkinson's, resulting in the loss of motor and other functions and so their protection is a key target of therapy,⁷³ and keto-diets improve motor function in rats with Parkinson's.⁷⁴

In mouse studies, ketogenic diets reduce the loss of motor neurons on amyotrophic lateral sclerosis (ALS or 'Lou Gehrig's disease) and reduce muscle wasting.⁷⁵ Similarly, a ketogenic diet reduces wasting in Huntington's disease.⁷⁶

Case study evidence is also beginning to show mood stabilising effects from the ketogenic diet used to treat type 2 bipolar disorder.⁷⁷

ⁱⁱ Technically BOHB is not a ketone body as the ketone moiety has been reduced to a hydroxyl group



Why do Ketones Have these Effects on the Brain?

Reduced inflammation

β -hydroxybutyrate directly reduces inflammation by suppressing activation of the NLRP3 inflammasome.⁷⁸ Interestingly, inflammatory messengers like tumour-necrosis factor alpha (TNF- α) might reduce the body's ability to produce ketones,⁷⁹ and so, taking exogenous ketone supplements, or MCTs might help the body to reduce inflammation, while also allowing there to be a better internal environment for ketogenesis.

Reduced accumulation of malformed proteins and plaques

Proteins (like tau-protein) in the brain become distorted (mainly due to hyperphosphorylation) and accumulate in the brains of Alzheimer's patients. These cause neuronal dysfunction and additional damage to neurons. These malformed and aggregated proteins are present in most people and can cause damage even if that person does not have Alzheimer's. These proteins and plaques (β -amyloid) present in AD and other neurodegenerations are reduced by ketogenic diets/ketones.

Improved fuelling

Almost all cells, except those lacking mitochondria, such as red blood cells, can also utilise lipid-derived fatty acids (via β -oxidation) and most cell types (such as neurons and cardiac tissue) have a high

affinity for ketone fuels. The entry of long-chain fats (the common dietary fats) into the brain and central nervous system tissue, is limited because the use of these fuels by neurons can cause hypoxia (lack of oxygen) and cell death. When the blood-brain barrier and cell membranes in the brain are damaged by trauma and injury though, or by endotoxicity and protein damage, long-chain fats can enter the brain and neurons, causing further injury. Interestingly astrocytes in the brain and CNS might 'scavenge' some of these fatty acids, to convert them to ketones for use as fuel, thus, preventing some of that damage.⁸⁰

Astrocytes in the brain and CNS 'scavenge' fatty acids to convert them to ketones for use as fuel

Glucose in excessive amounts is also undesirable, despite it being the main fuel for the brain. When glucose levels are consistently elevated, there is greater potential for *glycation* or damage to proteins caused when sugars 'stick' to proteins, which causes them to become dysfunctional. Ketones, on the other hand, are able to be used by neurons, without the raft of negative effects caused by long-chain fats and excessive carbohydrate intake.

Ketones are also protective against the effects of ischemia (loss of blood supply to



tissue),^{81, 82} and cell damage caused by hypoglycaemia.⁸³

Ketones are also protective against the effects of ischemia (loss of blood supply to tissue) and cell damage caused by hypoglycaemia

Reduced excitotoxicity and neurotoxicity

Ketones improve the *GABA to glutamate ratio*. Gamma-aminobutyric acid (GABA) is a relaxing neurotransmitter, conversely, glutamate is an excitatory neurotransmitter. When there is an imbalance of these (too much glutamate, and too little GABA), *excitotoxicity* occurs. Excitotoxicity refers to the overstimulation of neurons, especially by glutamate. This causes an increase in calcium uptake into neurons which in turn, signals the activation of various enzymes which in excess, damage DNA, cell membrane, and other structures directly, and by damaging cell membranes, allow additional damage to those cells. This toxicity is implicated in Alzheimer's, ALS, Parkinson's, Huntington disease, brain injury and concussion, multiple sclerosis, alcoholism, and drug withdrawal. Excitotoxicity is reduced by ketones and a ketogenic diet, and worsened by excessive

carbohydrate intake and rebound hypoglycaemia (low blood sugar, often caused by insulin resistance/pre-diabetes).⁸⁴

Neurogenesis

Ketones initially increase oxidative stress but a rapid adaptation, along with increased antioxidant activity and reduced excitotoxicity also results in increased brain-derived neurotrophic factor (BDNF).⁸⁵ This makes it highly likely that ketones can help the neurons of the brain to both survive, and to 'regrow' and repair.

Ketones can help the neurons of the brain to both survive, and to 'regrow' and repair.

What does this all mean?

Ketones provided by diet or supplements can help to support the healthy functioning of the brain and reduce damage to neurons. They provide fuel, reduce damage to neurons, and reduce the accumulation of plaques and proteins implicated in neurodegeneration. Furthermore, they help to reduce over-stimulation of the neurons and improve anxiety.



ALL ABOUT: NOOTROPICS

Key Findings:

- Caffeine-containing beverages are proven nootropics
- Common herbs like mint, sage, and others are likely to improve cognition
- Brahmi is a promising cognitive enhancer
- 'Brain-friendly' fats like medium-chain triglycerides and omega-3 fats are beneficial to brain health and function
- Nutrient support from a multi-nutrient can help to support cognition
- Emerging and compelling evidence suggests that mushrooms such as Lion's Mane could be potent cognitive enhancers

Nootropics are drugs, supplements, or foods and beverages that might improve cognitive functioning, including analytical functions, focus, mood, memory, creativity, and motivation. They are also known colloquially as smart drugs or cognitive enhancers (or cognitive 'boosters'). There are several drugs that are purported to improve memory and cognition, but increasing attention is being paid to nutritional supplements, herbs, and mushrooms that might improve mental functioning.

Nootropics fall under the umbrella of supplements which, although there may be some benefits to long-term brain health, are primarily designed to improve mental functioning to a better-than-normal state in the short-term, rather than treating a specific pathology or designed to improve function in the future, although commonly the same ingredients can accomplish several of these goals.

Nootropics are supplements designed to improve mental functioning to a better-than-normal state



Purported common nootropics

- Acetylcholine precursors (such as lecithin/phosphatidylcholine and citicoline)
- Acetyl-L-carnitine
- Astaxanthin
- Brahmi (*Bacopa monnieri*)
- Caffeine and other compounds from coffee, tea, and cocoa
- Ginkgo biloba
- Panax ginseng
- Multivitamins and minerals
- Sage (*Salvia officinalis*)
- Spearmint
- Lipids (especially DHA from fish oil and medium-chain triglycerides)
- Fungi (especially *Hericium erinaceus* – Lion's Mane)

These nootropics are common either as foods, supplements, or traditional medicines with a long history of use, but do they work?

Acetylcholine precursors

Acetylcholine was the first neurotransmitter identified by scientists and is the most abundant neurotransmitter in the peripheral, autonomic, and enteric nervous systems.⁸⁶ It is commonly referred to as the

'mind to muscle link' because it is the major neurotransmitter involved in signalling the muscles of the body to fire. It is also a major neurotransmitter in the brain, and it has been suggested that it is a key chemical for cognition and mental processes. A reduction in choline has been observed in the brains of people with Alzheimer's disease. While phosphatidylcholine from lecithin has been shown to reliably increase acetylcholine levels in mice,⁸⁷ reviews of the available research (consisting of two randomised trials) have suggested that lecithin doesn't improve cognition in Alzheimer's patients.⁴² However, citicoline (an intermediate in the creation of phosphatidylcholine from choline) is likely to improve cognition in both dementia patients and healthy people.⁴²

Citicoline is likely to improve cognition in both dementia patients and healthy people

Acetyl-L-carnitine

Acetyl-carnitine is a naturally occurring substance formed in cells when an acetyl group is added to carnitine. Carnitine (created from the amino acid lysine) aids the transport of fatty acids into the mitochondria to be used for energy. Acetyl-carnitine is more easily absorbed and can cross the blood-brain barrier more easily than L-carnitine. Acetyl-L-carnitine has been



shown to reduce fatigue, anxiety and depression, and age-related cognitive defects.⁴²

Acetyl-L-carnitine has been shown to reduce fatigue, anxiety and depression, and age-related cognitive defects

Astaxanthin

Astaxanthin is a red-orange carotenoid found mostly in several species of krill, shrimp, algae, and some lichen. Early research suggests that taking an astaxanthin supplement (6mg astaxanthin and 10mg sesamin) daily for 12 weeks could improve psychomotor speed and processing speed in people with mild cognitive impairment.⁸⁸

Bacopa monnieri

Bacopa monnieri (water hyssop, brahmi, Indian pennywort) is a perennial creeping herb native to India, Australia, Europe, Africa, Asia, and the Americas. It is a traditional Ayurvedic medicinal herb with use as a cognition and memory enhancer.⁴³ Several studies have demonstrated the potential for brahmi to improve cognition. It is thought to do so by antioxidant neuroprotection, increasing choline, reducing β -amyloid, increased cerebral blood flow, and by modulating

neurotransmitters such as acetylcholine, serotonin, and dopamine.⁴³ In a 2008 randomised controlled trial, 160 mg brahmi extract (equivalent to 4 g dried herb) given to volunteers for 90 days, resulting in significant improvements to memory accuracy.⁴⁴ A recent (2014) meta-analysis has summarised the findings from nine existing studies (437 participants), showing improved cognition and reaction times.⁴⁵

Caffeine

Caffeine is a well-known cognitive enhancer. Reviews of the evidence show that caffeine improves attention, vigilance, reaction times, and problem-solving (especially in sleep-deprived people).^{19, 20}

Caffeine improves attention, vigilance, reaction times, and problem-solving

Large scale reviews of the evidence show significant benefits from caffeine for positive mood and lower perceived fatigue. Doses of 12.5 mg up to 400-600 mg (<1 to 4-6 cups per day of coffee) provide a positive effect,^{20, 21} however, greater doses do not always provide greater benefits to cognition and mood, and typically, the first cup provides the majority of benefits.²¹ Interestingly, habitual users appear to experience *greater* cognitive or mood effects compared with low/non-users.²¹



Tea and coffee both produce similar benefits to mood and cognition.²¹ In addition to its acute effect on mood and cognition, caffeine-containing beverages may be protective against cognitive decline and dementia.²²

Other constituents from tea

Tea constituents other than caffeine (L-theanine and epigallocatechin gallate) might also improve cognition. A review of the research in this area suggested that caffeine combined with theanine (as found in tea) improved alertness and attention more than caffeine alone.⁸⁹

Ginkgo biloba

Ginkgo (the maidenhair tree) is one of the most ancient species of tree in existence and has a long history of use in traditional medicine and as a food.

While the use of Ginkgo is extremely common for cognitive improvements, several earlier reviews have found no convincing evidence from randomised trials for a meaningful effect on cognition from ginkgo.^{90, 91} A 2009 Cochrane Database review concluded, "Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo." But the "evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable."⁹²

However, more recent (2014 & 2016) reviews suggest a more positive role for ginkgo extracts for cognition in cognitive decline. In a review of nine trials, it was concluded that ginkgo extract at a dose of 240 mg/day is "able to stabilize or slow decline in cognition, function, and behaviour" in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.⁴⁶ In a review of 21 trials with 2608 patients, Ginkgo biloba (in combination with conventional medicine) was superior in improving Alzheimer's and cognitive impairment scores (at 24 weeks) to control.⁹³

Ginseng

Ginseng is the root of the Korean Ginseng (*Panax ginseng*) plant. This root has a long history in traditional medicine as an anti-stress and nervous 'tonic' purported to improve cognition. Studies have suggested that ginseng might improve cognitive performance,⁹⁴ and this effect could be related to one of the known effects of ginseng, which is to help modulate blood sugar levels.^{95, 96} While other studies show a trend towards improved cognition from ginseng, a lack of consistency among studies reduces the ability to draw conclusions from them as a whole.⁹⁷

Ginseng/Ginkgo combination

The use of ginseng and ginkgo in combination has also been studied in healthy adults. A dose-dependent effect on



memory was found (320-960 mg of combination vs placebo).⁹⁸

Multivitamins

In an 8-week placebo-controlled trial, a standard over-the-counter multivitamin and mineral supplement resulted in significant improvements to contextual recognition and memory performance. Similarly, in a study of school-age children in India, 5 out of 7 memory tests were improved significantly for those taking a multi- versus control.²⁷ In a study of healthy women over 50, it was found that even a single dose of a multivitamin reduced depression and anxiety, and stress scores several hours after supplementation.²⁸

Sage

Sage or *Salvia officinalis* is a perennial, evergreen herb common in culinary and medicinal tradition. Sage contains a large array of compounds that may have cognitive effects including caffeic acid, rosmarinic acid, salvianolic acids, sagecoumarin, lithospermic acid, sagerinic acid, yunnaneic acids, luteolin, apigenin, hispidulin, kaempferol, quercetin, a and b-thujone, camphor, 1,8-cineole, ahumulene, b-caryophyllene, viridiflorol, carnosic acid, ursolic acid, carnosol, and tanshinones. Evidence from in vitro and animal studies suggests that these compounds in sage could improve cognition by reducing amyloid- β (found in higher amounts on Alzheimer's and other neurodegenerative disorders), increasing choline, reducing anxiety, reducing oxidation and

inflammation, and encouraging neuronal repair.⁴⁷ In studies of healthy people, a single dose of sage has resulted in improved memory scores and mood, alertness and attention, calmness, and overall cognition.^{47, 48}

In studies of healthy people, a single dose of sage has resulted in improved memory scores and mood, alertness and attention, calmness, and overall cognition

Daily use of sage supplements has also been studied. A non-randomised, non-blinded, within-subject study was conducted for 28 days in 14 healthy people (18-40 years). At the completion of the study, significant improvements were seen for reaction time, cognitive accuracy, attention, and short term and working memory.⁴⁹ Another trial including cognitive function in perimenopausal women found a significant reduction in time for a common cognitive test (Stroop colour test).⁵⁰

Spearmint

Spearmint (*Mentha spicata*) is another common herb with purported cognitive effects.



Spearmint extracts (>14.5% rosmarinic acid and 24% total phenolic content) have resulted in improved cognitive scores in several studies. (Interestingly, rosmarinic acid is also common in other herbs such as rosemary, for which it is named, and thyme). In a 90-day randomised, double-blind, placebo-controlled trial, in healthy, active men and women, 900 mg of spearmint extract significantly improved reactive agility.⁵¹

Lipids and 'smart fats'

Omega 3 fats

The omega 3 fats DHA and EPA play an important role in brain development and healthy functioning of the brain and central nervous system. DHA, in particular, makes up the majority of the polyunsaturated fat content of the brain, comprises over 50% of the plasma membrane of neurons, and is essential to the functioning of the brain and optimising cognition and mood.¹²

Omega-3 fats are linked to reduced mental fatigue,¹³ improved memory and cognition and reduced cognitive decline,^{14, 15} reduced rates of depression and improved structural integrity of the brain.^{16, 17} Additionally, DHA improves cognition and behaviour in children.⁹⁹

Medium-chain triglycerides

Medium-chain triglycerides (MCT) are naturally occurring fats found in small amounts in dairy products and greater amounts in coconut oil. They are also commonly used as isolated supplement

oils. MCT supplemented diets improve mental performance in those with Alzheimer's Disease and age-related cognitive decline,^{29, 30} and a single dose of 20 g MCT has been shown to improve cognition.³¹

Exogenous ketones?

Exogenous ketone supplements provide BOHB directly to the body without requiring ketogenesis and without concurrent elevations in free fatty acids.¹⁰⁰ They are considered to be a safe and effective way to increase ketone body concentrations,¹⁰¹ and are being studied for their use as potential treatments for brain injury,¹⁰² cancer,^{103, 104} Angelman syndrome,¹⁰⁵ and Alzheimer's disease,¹⁰⁶ amongst other conditions.

Exogenous ketone supplements are available as either salts or esters of BOHB. Supplements containing ketone salts are some combination of sodium-, magnesium-, calcium or potassium-BOHB, and are available commercially from several companies under patent.¹⁰⁷ Ketone esters have only recently become available for use by the public but are not common at the time of writing and are prohibitively expensive. Both ketone esters and salts elevate BOHB to levels consistent with NK.¹⁰⁸ Ketone esters increase ketone levels more than equivalent amounts of ketone salts with fewer gastrointestinal symptoms per increment of increase.¹⁰⁹

Ketone supplements have positive effects on anxiety,¹⁰⁶ mental performance and memory,¹⁰⁶ and reduce inflammation by



suppressing activation of the NLRP3 inflammasome.⁷⁸ Ketones show promise for helping to treat many of the underlying causes of neurodegeneration cognitive decline.

Elevated ketones reduce the glutamate-GABA imbalance which can commonly result in excessive stress and fatigue.¹¹⁰ They also have been shown to help reduce the formation and accumulation of brain-damaging misfolded proteins (such as tau proteins and amyloid- β) seen in neurodegenerative disorders like Alzheimer's disease and dementia.¹⁰⁶ Animal studies further suggest the utility of ketones to help reduce anxiety,¹⁰⁶ and improve learning and memory.¹⁰⁶

Other ketogenic supplements?

Many supplements are purported to be ketogenic (increasing the internal creation of ketones) including leucine, lysine, short-chain fatty acids, and medium-chain triglycerides (MCTs). Of these, leucine and lysine have limited effects on ketone levels. There is also limited evidence in humans for the effect of short-chain fats (such as acetic acid from vinegar, or butyric acid), however, they are likely to be ketogenic and might be more so than MCT.⁵⁴ The most compelling evidence currently exists for the use of MCTs for ketogenesis, as they reliably and consistently increase ketone concentrations in the blood in a dose-dependent fashion,⁵⁴ and exogenous ketones reliably increase

ketones without encouraging ketogenesis *per se*.

Fungi

Hericium erinaceus (also called lion's mane mushroom) is an edible and medicinal mushroom native to North America, Europe and Asia belonging to the tooth fungus group. Lion's Mane has been shown to increase 'Nerve Growth Factor',³² which helps nerves and brain cells to grow and repair.³³⁻³⁸ Because of this brain-repair effect, Lion's Mane is being considered as one of the most promising preventative treatments for Alzheimer's Disease and dementia.^{39, 40} It's also been demonstrated to significantly reduce depression and anxiety after 4 weeks of treatment,³⁴ and to improve cognitive function.⁴¹ Lion's Mane might also improve physical performance by reducing perceived fatigue.¹¹¹

Other mushroom types, especially Turkey Tail (*Trametes versicolor*), Cordyceps (*Ophiocordyceps sinensis*), and Reishi (*Ganoderma lucidum*) are also suggested as benefiting neural health and cognition.

Conclusion

There is no substitute for a good diet, improved sleep, exercise, and living a life of balance, but some supplements can likely provide a boost to your brainpower and offer other, longer-term health and cognitive benefits. The strongest evidence exists for caffeine-containing beverages like coffee and tea, and from nutrient-rich herbs like mint, sage, brahmi, and others such as



rosemary and thyme. Additionally, emerging benefits from fungi, most especially Lion's Mane, but also others like Turkey Tail (*Trametes versicolor*) and Reishi (*Ganoderma spp.*) support a powerful effect on cognition. Also, ensuring nutrient density

from a quality multivitamin/mineral will help to support cognition, along with providing brain-friendly lipids; MCTs and the omega-3 fats (especially DHA).



RESEARCH IN BRIEF

Is Evening Primrose Oil worth taking?

Reviews of the evidence have shown that there is little meaningful evidence to support the use of evening primrose oil (EPO) for breast tenderness or dermatitis.^{112, 113} But one review has suggested a benefit (versus drugs used for treatment) for breast pain. It should be noted that the studies cited within these reviews still offer many conflicts.¹¹³

There is only limited data on the use of primrose oil for schizophrenia but a Cochrane review of this application found no clear effect of EPO supplementation on schizophrenia.¹¹⁴

Primrose oil is probably not worth taking

What is the evidence behind the 'Palaeolithic Ketogenic Diet'?

The *Palaeolithic ketogenic diet* is a version of the popular paleo diet. While 'paleo' typically involves the removal of processed and unrefined foods, along with grains, legumes, and dairy, typically, tubers and fruit are

allowed. In the Palaeolithic ketogenic diet, these obligate carbohydrate foods are removed to bring the diet into line with a ketogenic diet that is higher in fat and very low in carbohydrate. It differs from a standard ketogenic diet in that it disallows dairy, which can be a common allergen, especially for people with autoimmune or inflammatory disorders.

[See [Is Dairy Inflammatory?](#)]

Case studies have shown promising results from the paleo-keto approach for Crohn's disease, Gilbert's syndrome,¹¹⁵ and childhood epilepsy.¹¹⁶

Case studies have shown promising results for Crohn's disease, Gilbert's syndrome, and childhood epilepsy

In one case, the diet resulted in complete remission from symptoms of Crohn's disease, which was maintained.¹¹⁷

In other cases, insulin function was restored in two patients with type 1 diabetes (a 19 years adult and a child).^{118, 119} Similarly, a patient with type 2 diabetes was able to normalise high blood pressure and discontinue medications while also reducing triglycerides and blood glucose.¹²⁰

It should be noted that the improvement in glucose and triglycerides were not meaningful but the patient had also ceased



medications that were previously helping to control this.

Insulin function was restored in two patients with type 1 diabetes

The diet has also stabilised disease activity or reduced tumour size in several cancer patients,¹²¹ and resulted in the complete cessation of cervical intraepithelial neoplasia (pre-cancer of the cervix) after 26 months on paleo-keto.¹²² A patient with rectal cancer following paleo-keto improved markers and lab findings for 5 months. Following this (apparently) adherence worsened and surgery was needed at 24 months.¹²³

While the case study evidence is promising, further randomised controlled trials need to be performed to compare this diet to others. The cases appear to indicate that people can achieve additional benefits to either paleo or a keto approach alone by following a 'paleo-keto' approach and this is likely to be due to two major factors:

1. When people following keto eliminate dairy, they may identify an underlying intolerance to dairy proteins
2. When people following paleo go low-carb, they may achieve benefits of carb-restriction if they are insulin resistant or have a medical condition that benefits from carbohydrate restriction.

As such, it is also highly likely that while some people will benefit from a paleo-keto approach, the additional restrictions may not be necessary for many. If a paleo approach is working well for you, stick with it! Similarly, if a keto approach (including dairy) is working for you, there is no need to change. And if you'd like to try a paleo-keto approach to see how it feels, there's nothing wrong with that either.

Do saunas help detoxification?

While saunas are known to be beneficial to health (by inducing 'heat shock proteins') and might even aid hypertrophy (muscle growth), the evidence for a 'detox' effect is less clear. It is plausible, as the skin is a major excretory organ and can help the body to eliminate toxins, and the increased metabolic activity and catabolic processes initiated by heat-shock proteins may amplify this.

research is lacking although a few studies have shown some isolated findings for an effect of saunas on detox



At this stage though, research is lacking although a few studies have shown some isolated findings for an effect of saunas on detox, including improved healthy questionnaire scores and reduced neurotoxicity findings.^{124, 125}

Does the amount of carbohydrate in the diet affect metabolic syndrome risk?

Carbohydrate intake and risk of metabolic syndrome: a dose-response meta-analysis from observational studies

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Highlights

- Carbohydrates intake is associated with more likelihood of having metabolic syndrome.
- Linear dose-response relationships were found, with a 2.6% increase in the risk of metabolic syndrome per 5% energy intake from carbohydrates.
- Association between carbohydrates intake and risk of metabolic syndrome appears to be affected by region.

Abstract

Background and Aims

Epidemiological association studies have shown inconsistent findings between carbohydrate intake and the risk of metabolic syndrome. Therefore, we aim to conduct the first dose-response meta-analysis to investigate this effect.

Methods and Results

A systematic search in PubMed and Web of Science databases throughout June 01, 2019, together with relevant literature scrutiny, was performed to identify related studies for inclusion into the study. We calculated the odds ratios (ORs) with 95% confidence intervals (CIs) using a random effect model. Furthermore, subgroup, sensitivity, heterogeneity, and publication bias analyses were performed. This meta-analysis included 14 cross-sectional and four cohort studies, totalling 284,638 participants and 69,554 metabolic syndrome cases. The highest versus the lowest carbohydrate intake values were associated with increased risk of met. syndrome (OR: 1.253, 95% CI: 1.147-1.368), with moderate heterogeneity ($I^2=54.5\%$). Using dose-response analysis, we found a linear association between carbohydrate consumption and met. syndrome risk with a corresponding OR of 1.026 (95% CI, 1.004-1.048) and with significant heterogeneity ($I^2=82.0\%$) at 5% energy from carbohydrate intake. We have found similar results using subgroup analyses for major study characteristics and adjustment for



confounders. Sensitivity analysis further enhanced the robustness of the results, and no publication bias was detected.

Conclusion

Carbohydrate intake is associated with an increased risk of developing metabolic syndrome. Therefore, additional large prospective cohort studies are warranted to confirm our findings.¹²⁶

Comment

In first reading the title of this study, you might be forgiven for thinking, 'yeah, no shit...' but this is important and informative to the scientific debate around carbs vs fat and protein.

As a systematic review and meta-analysis, it combines many studies featuring hundreds of thousands of participants, and thus, has significant strength to show robust associations between dietary inputs and health outcomes. But, like all observational data, it does suffer from shortcomings as there was no intervention being compared to a control or placebo, and no *control* over what the participants did and didn't do. This means that there is a large potential for *confounding* and other lifestyle factors could influence the findings. For example, those who eat the most carbohydrate might be consuming sugary drinks, or other processed foods that happen to be higher in carbohydrate content (but are comparatively *nutrient-poor* and are independently associated with poor health outcomes.) It is also possible that those

choosing to eat higher carbohydrate diets have poorer health habits and might smoke and drink more, or exercise less. It would be unlikely if this were the case though. Typically, those with healthier habits have been *more inclined* towards a higher carbohydrate intake because that has been the prevailing dietary guidance.

Typically, those with healthier habits have been *more inclined* towards a higher carbohydrate intake because that has been the prevailing dietary guidance

In fact, up until very recently, dietary guidelines specifically for those with diabetes and metabolic syndrome were high-fat, low-carbohydrate diets. So, we most often see in cohort studies, that those who tend to eat fewer carbohydrates (and more meat in particular) are those who are change-resistant, and they concomitantly have higher rates of smoking, drinking, and obesity.

[\[See this previous issue of CARR\]](#)

So, the findings of this study seem to be stronger than those that suggest we should reduce meat for very small improvements in risk (<10%).



In this research, the highest vs lowest carbohydrate intakes resulted in a 25% increased risk of metabolic syndrome and ~3% increase in risk per 5% increase in total energy from carbohydrate (i.e. moving from a 30 to 35% carbohydrate diet).

Overall, the 'state of the nation' remains generally the same though. Excessive amounts of processed and refined foods (which are generally those high in sugar and refined carbohydrate) are the factor most associated with worse health outcomes. Eating unrefined foods, on the other hand, is the proven way to reduce disease risk.

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