Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Psyllium

Evidence Summary

Psyllium may modestly reduce dementia risk factors such as LDL-c, body weight, and glucose indices. It is generally well-tolerated, and side effects can be reduced through appropriate use.

Neuroprotective Benefit: There is little to no evidence that psyllium can be directly neuroprotective. Psyllium may be indirectly neuroprotective by improving other health indices.

Aging and related health concerns: Psyllium supplementation is associated with moderate reductions in LDL-c, and may reduce blood sugar, HbA1c, body weight, and improve other lipid profiles.

Safety: Psyllium is used as a food additive and is typically thought to be safe. Side effects include intestinal symptoms, and rarely, anaphylactic allergy and bowel obstruction. Supplements should be checked for lead levels.

Availability: OTC	**Dose**: Varies on indication; typical use can be 5 to 10 grams of psyllium up to 3 times a day. Doses are taken orally and must be taken with adequate hydration, typically at least 8 ounces of fluids.
Half-life: N/A	**BBB**: Not penetrant
Clinical trials: The largest meta-analysis identified included a total of 2,769 participants.	**Observational studies**: The largest observational study that delineated psyllium users vs. users of other dietary fibers included 4,383 women who used psyllium.

What is it?

The plant genus *Plantago* contains approximately 200 species of plants. Several members of *Plantago* genus are commonly called psyllium (Franco et al., 2020). Seeds – or, more accurately, the seed husks – from these different species collectively known as psyllium contain hydrophilic polysaccharides that can absorb a significant amount of water, forming a viscous, soluble gel. By absorbing water in the gut, psyllium increases fecal weight and improves stool consistency, thus potentially alleviating constipation symptoms. Psyllium is also thought to influence the gut microbiome, which can have wide-ranging impacts. Through these effects on gut function and health, psyllium is thought to lower LDL-c, improve blood glucose measures, and may assist in management of weight and blood pressure (Belorio & Gómez, 2020).

Psyllium is often used as a food additive, and for products that contain at least 1.7 grams of soluble fiber per serving, the FDA has allowed the health claim that states "diets that are low in saturated fat and cholesterol and that include soluble fiber from psyllium seed husk may reduce the risk of heart disease".

Through the effects of psyllium on lipid profiles, glucose metabolism, body weight, and blood pressure – all of which can influence risk of dementia – psyllium may also ultimately impact dementia risk.

It is worth noting that some sources use other names such as ispaghula, Plantago ovata, and psyllium husk instead of psyllium. For clarity, this report will refer to this supplement only as psyllium.

Neuroprotective Benefit: There is little to no evidence that psyllium can be directly neuroprotective. Psyllium may be indirectly neuroprotective by improving other health indices.

Types of evidence:

- 1 Cochrane review
- 2 randomized controlled clinical trials
- 2 observational studies
- 2 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical trials have tested whether psyllium can prevent dementia, decline, or improve cognitive function.

Psyllium is thought to potentially improve health indices such as cholesterol, blood sugar, and body weight that are all well-established risk factors for dementia (Livingston et al., 2024). It is theoretically possible that indirectly, intake of psyllium could attenuate some level of risk for dementia in at least certain populations by modulating their existing risk factors.

Intake of other fiber supplements such as inulin have been associated with some improvements in cognition in cognitively intact populations (Lochlainn et al., 2024). While the fiber supplements studied by Lochlainn et al., 2024 are different than psyllium and were selected for their prebiotic potential, it nonetheless provides a theoretical framework on which psyllium could impact brain health. However, this remains in the realm of speculation; clinical trials are required to assess whether psyllium may have any cognitive benefit for any population.

Human research to suggest benefits to patients with dementia:

There is no research to suggest that psyllium provides benefits to patients with dementia.

Psyllium may be contraindicated for patients with dementia. Maintaining adequate fluid intake alongside psyllium is important to reduce risk of bowel obstruction, and it can be difficult for individuals

with significant cognitive impairment to consume enough liquid. Moreover, psyllium can pose a choking risk, which can be a concern for patients who are unable to coordinate swallowing.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Psyllium likely has an indirect mechanism of action for neuroprotection, particularly as it is not thought to be absorbed systematically (Drugs.com). As described in the 'Aging and Related Health Concerns' section below, use of psyllium may improve lipid profile, blood pressure, body weight, and blood sugar indices, all of which could reduce risk of dementia (Livingston et al., 2024). There is some initial evidence that dietary fiber intake may be positively correlated with cognitive function (Sun et al., 2022). However, dietary fibers can have very different profiles and effects. No published studies have yet reported associations between psyllium specifically and neuroprotection in humans.

Two preclinical studies have suggested that psyllium supplementation can have neuroprotective effects. One group tested the effects on cognition of exercise and/or psyllium in a rat model of diabetes. While the combination therapy had the strongest positive effects, diabetic rats who received psyllium alone did have some cognitive improvements in passive avoidance memory, exploratory behavior, locomotor activity, and non-spatial cognitive memory compared to diabetic rats who did not receive exercise training or psyllium. The authors hypothesized that the effects of psyllium could be due to the improvements in triglycerides, LDL-c, VLDL-c, cholesterol overall, and glucose homeostasis seen in animals treated with psyllium (Parsa et al., 2021). Another study found that arabinoxylan, a polysaccharide that is abundant in psyllium, was neuroprotective in an animal model of vascular dementia. In their follow-up study, rats were given placebo or different doses of psyllium and then received surgery that is used as a model of chronic cerebral hypoperfusion. They found that animals who received at least 10 mg/kg daily of psyllium had significantly reduced white matter damage, myelin damage, microglial activation, and astrocyte activation (Lim et al., 2019).

The mechanism(s) of action at play in the latter study are less clear, as psyllium is generally not thought to be systemically absorbed. And as psyllium is less fermentable than other dietary fibers, fewer metabolites such as short-chain fatty acids are produced from psyllium than from other dietary fibers. However, compounds like arabinose and short-chain fatty acids like butyrate can be released from psyllium in the gut. These metabolites can be absorbed into systemic circulation and may affect the brain (Lim et al., 2019). Psyllium is thought to be a prebiotic; that is, it may help facilitate the growth of beneficial bacterial species, and protect against the growth of undesirable species. Experiments in cell

and animal models indicate that fibers that contain arabinoxylans, like psyllium, can inhibit the release of IL-8 and TNF-α that are induced by lipoproteins, and that psyllium may improve intestinal barrier function and immune function. At least one study in humans has also suggested that psyllium supplementation may be associated with decreased levels of TNFα (Kamalpour et al., 2018).

Psyllium has other actions which could have an indirect impact on brain health. Psyllium may modulate glucose uptake and reduce peak postprandial blood glucose levels as well as increase fatty acid oxidation in skeletal muscles (Togawa et al., 2013; McRorie et al., 2021). Usually, nutrients are absorbed in the early small intestine, but psyllium can slow absorption. This means that more nutrients reach the distal small intestine, which can release glucagon-like peptide1 (GLP-1) into the blood stream. GLP-1 can have several beneficial systemic effects. Psyllium can modulate cholesterol levels by sequestering bile acids, which has downstream effects of lowering LDL-c without affecting HDL-c. Psyllium also can promote feelings of satiety and slow gastric emptying, which can suppress appetite (McRorie et al., 2021). All these actions on the metabolic system could indirectly affect brain health.

However, these data are either preclinical, not directly linked to brain health, or both. Significant research is required to explore whether psyllium is beneficial for neuroprotection.

APOE4 interactions:

It is not known whether the impact of psyllium supplementation is impacted by APOE status

Aging and related health concerns: Psyllium supplementation is associated with moderate reductions in LDL-c, and may reduce blood sugar, HbA1c, body weight, and improve other lipid profiles.

Types of evidence:

- 12 meta-analyses or systematic reviews
- 3 randomized controlled clinical trials
- 1 open label study
- 1 observational study
- 4 reviews
- 1 laboratory study

The best characterized use for psyllium is as a bulk forming laxative for constipation. Psyllium has been studied for its impact on cardiovascular health and on glucose metabolism.

Cardiovascular Indices: BENEFIT

Use of psyllium can improve certain measures of cardiovascular health, which may help prevent or treat cardiometabolic disease (Chen et al., 2022). Based on the available evidence of benefit, both the US FDA and Health Canada allow foods containing certain amounts of psyllium to state certain health claims. The US FDA allows health claims stating that "diets that are low in saturated fat and cholesterol and that include soluble fiber from psyllium seed husk may reduce the risk of heart disease" (FDA), while Health Canada allows stating that specific serving sizes of specific brand names 'with psyllium supplies/provides [the applicable percent] of the daily amount of the fibres shown to help reduce/lower cholesterol" (Health Canada).

Lipid Profile

A systematic review of systematic reviews and meta-analysis examined the effects of food on LDL-c levels. The study found high grade evidence that compared to low fiber diets or diets with insoluble fiber, 11 grams a day of psyllium was associated with moderate reductions in LDL-c (Schoeneck & Iggman, 2021).

Jovanovski et al., 2018 was one systematic review included by Schoeneck & Iggman, 2021, and contained the data that Schoeneck and Iggman utilized for their findings on psyllium. Jovanovski and colleagues included 28 RCTs lasting at least 3 weeks that looked at the effects of psyllium on lipid profiles in 1924 participants with or without hypercholesterolemia. They found that compared to control, use of a median dose of approximately 10 grams daily of psyllium was associated with significant reductions in LDL-c (MD=-0.33 mmol/L; 95% CI -0.38 to - 0.27 mmol/L; $p<0.00001$), non-HDL-c (MD= -0.39 mmol/L; 95% CI -0.50 to -0.27 mmol/L; $p<0.00001$), and apoB (MD =-0.05 g/L; 95% CI -0.08 to - 0.03 g/L; $p<0.0001$). The quality of evidence was graded as moderate for LDL-c and non-HDL-c, and as high for apoB. The authors note that more studies in patients without high cholesterol are needed to better assess the impacts of psyllium on those populations.

A 2024 systematic review and meta-analysis included 2,769 participants of varying health statuses, from healthy to T2D to hypertension to hypercholesterolemia. They ranged in age from 27 to 69, and the

dosage of psyllium ranged from 2 to 20.4 grams per day. The meta-analysis found that compared to control group, individuals who received psyllium had significantly lower total cholesterol levels (WMD=-0.28 mmol/L; 95% CI -0.36 to -0.20; p<0.0001), though there was significant heterogeneity. Psyllium supplementation was associated with a significant reduction in LDL-c compared to control (WMD=-0.35 mmol/L; 95% CI: -0.54 to -0.16; p=0.0004), also with significant heterogeneity. There was no significant difference between treatment groups for HDL-c overall, but subgroup analyses suggested that psyllium was associated with a significant decrease in HDL-c in patients with lipid disorders. There was no significant difference in triglycerides between the groups (Zhu et al., 2024).

Xiao et al., 2020 includes a meta-analysis of 8 studies (n=395) in patients with T2D treated with a mean dose of 9 grams a day with a range 3.4 to 15 grams a day, for a mean of 12 weeks with a range of 8 weeks to 20 weeks. Their meta-analysis found that compared to the control group, psyllium reduced levels of triglycerides (weighted mean difference (WMD)= -19.18 mg/dl; 95% CI -31.76 to -6.60), with significant heterogeneity that may be due to dosing. Compared to control, psyllium supplementation was associated with a significant reduction in LDL-c WMD= -8.96 mg/dl; 95% CI -13.39 to -4.52), with significant heterogeneity that may be due to duration of intervention. They did not find any differences in total cholesterol levels or HDL-c.

Blood Pressure

A 2024 systematic review and meta-analysis examined the impact of psyllium on blood pressure. The study included 14 RCTs and a total of 802 participants between the ages of 26 and 51 years. Doses of psyllium ranged from 7 to 25 grams a day. Compared to placebo, psyllium supplementation significantly decreased systolic blood pressure (WMD=-2.24; 95% CI -3.13 to -1.35; p<0.05); the impact on diastolic blood pressure was not significant (Gholami & Paknahad, 2024).

Clark et al., 2020 also assessed the effect of psyllium supplementation on blood pressure. They included 11 RCTs of 592 participants. The participants ranged in age from 25 to 70, had various diagnoses from T2D to hypertension to hyperlipidemia. The interventions lasted from 4 weeks to 6 months, and daily dosage varied from 3.7 grams to 15 grams. Their meta-analysis found that participants who received psyllium had significantly lower systolic blood pressure (WMD=-2.04; 95% CI -2.82 to -1.63; p<0.001) but there was no significant effect on diastolic blood pressure. They also performed a meta-regression analysis that indicated that there was a stronger hypotensive effect in patients with higher systolic and/or diastolic blood pressure.

Body Weight

Supplementation with psyllium may lead to modest decreases in body weight, though there are some conflicting findings. A network meta-analysis of different nutraceuticals and body weight found moderate certainty evidence that psyllium can lead to statistically significant weight loss compared to placebo (mean difference=-3.70 kg; 95% CI -5.18 to -2.22), though this significant effect was not seen in trials lasting more than 12 weeks (Shahinfar et al., 2023).

A 2023 review and meta-analysis assessed RCTs in individuals with overweight or obesity; the included RCTs were of just psyllium rather than combination approaches, were at least 2 months long, involved doses of at least 7 grams a day that were taken before or with meals, and had consistent background diets throughout the study. The average duration of the studies was approximately 4 to 5 months. Ultimately, 6 studies were included, comprising 354 participants. This study found that psyllium resulted in statistically significant decreases in body weight (MD=-2.1 kg; 95% CI -2.6 to -1.6; $p<0.001$), with no indication of heterogeneity. There were commensurate, statistically significant decreases in BMI and waist circumference (Gibb et al., 2023).

Both Mofrad et al., 2020 and Xiao et al., 2020 detail systematic reviews and meta-analyses that find no change in weight loss after psyllium supplementation. However, Gibb et al., 2023 discusses methodological characteristics of the above two studies that might explain the discrepancies. For instance, Mofrad et al., 2020 included some studies that were less than 4 weeks long, and might not have been enough time to observe weight loss; Mofrad et al., 2020 also performed subgroup analyses that indicated that higher doses of psyllium over longer durations were associated with significant reductions in body weight. In Xiao et al., 2020 included only 3 studies that assessed weight. Moreover, one study in the weight loss analysis of Xiao et al., 2020 indicated that psyllium group had gained weight compared to control, but this appears to be an error or otherwise not a direct comparison to the other studies; in the original publication by Soltanian & Janghorbani, 2019, patients received either flaxseed, psyllium, or placebo, and while patients who received flaxseed lost significantly more weight than the psyllium group, patients who received either flaxseed or psyllium both lost significantly more weight than the placebo group.

Diabetes and Blood Sugar Indices:

A 2024 systematic review and meta-analysis of RCTs assessed the impact of psyllium use on various blood sugar indices. The meta-analysis included 19 trials and comprised 962 participants in total. The participants ranged in age from 24 to 77 years, and the dosages of psyllium were from 0.002 to 25 grams a day. The meta-analysis found that compared to the control or placebo group, the group who received psyllium had significant decreases in fasting blood sugar (WMD=-6.89; 95% CI -10.62 to -3.16; p<0.001), $HbA1_c$ (WMD=-0.75; 95% CI -1.21 to -0.29; p<0.001), and insulin resistance as measured by the homeostatic Model Assessment of Insulin Resistance (HOMA IR) (WMD=-1.17; 95% CI -2.11 to -0.23; p<0.05). There was significant heterogeneity for the difference in fasting blood sugar, $HbA1_c$, and HOMA IR; the results were more robust for fasting blood sugar levels and $HbA1_c$. Overall, the quality of this evidence was categorized as moderate. Subgroup analyses indicated that psyllium consumption of at least 10 grams a day was needed for significant differences in $HbA1_c$ and insulin resistance, and while all doses were associated with improvements in fasting blood sugar, interventions needed to be at least 50 days for benefit on fasting blood sugar. Insulin levels were not significantly affected by psyllium supplementation (Gholami et al., 2024).

Studies have also specifically examined the effects of psyllium in patients with type 2 diabetes (T2D). Xiao et al., 2020 is one such systematic review and meta-analysis; they found that in their six included studies, patients who received psyllium compared to control had significant decreases in fasting blood sugar (WMD=-31.71 ml/dl; 95% CI -50.04 to -13.38), and $HbA1_c$ (WMD= -0.91%; 95% CI -1.31 to -0.51), both with significant heterogeneity. Another meta-analysis (n=35 studies) in patients without diabetes, patients at risk of T2D, and patients with T2D, found that there were no significant changes in fasting blood sugar or $HbA1_c$ for euglycemic patients. There was a modest benefit to prediabetic patients, and for patients with diabetes, psyllium dosing before meals was associated with significant decreases in fasting blood sugar (MD=-37.0; 95% CI -55.4 to -18.7, p<0.001) and $HbA1_c$ (MD=-0.97%; 95% CI -1.94 to -0.01, p=0.048) (Gibb et al., 2015).

Other diseases:

Dietary fiber and/or psyllium specifically have been suggested to be beneficial for maintaining remission in ulcerative colitis, colon cancer prevention, and gastroesophageal reflux (Hosseini et al., 2018; Belorio & Gómez, 2020; Przybyszewska et al., 2024), though there is conflicting evidence for the former two conditions. For instance, one Cochrane review of dietary fiber for prevention of recurrence of colorectal

adenomas and carcinomas found one study that reported an increase in recurrence of adenomas in patients who received psyllium (called ispaghula husk in this publication) compared to controls, though their sensitivity analyses indicated that missing data might affect this finding (Yao et al., 2017). A longitudinal study in postmenopausal women found that there was no association between colorectal cancer risk and soluble prebiotic fiber such as psyllium (Skiba et al., 2019). More studies, particularly RCTs, would be needed to fully explore whether psyllium use influences risk of colon cancer or recurrence, or other gastrointestinal health conditions. Psyllium has also been suggested to be potentially beneficial in MASLD/MASH (Stachowska et al., 2020).

Safety: Psyllium is used as a food additive and is typically thought to be safe. Side effects include intestinal symptoms, and rarely, anaphylactic allergy and bowel obstruction. Supplements should be checked for lead levels.

Types of evidence:

- 1 meta-analysis or systematic review
- 2 clinical trials
- 2 professional resources
- 4 reviews

Psyllium is commonly used as a food additive and is generally thought to be safe with appropriate use. The most common side effects are stomach cramps, bloating, diarrhea, flatulence, and intestinal discomfort (Sheer & Alois, 2024). These symptoms may be mitigated by starting with smaller doses and titrating up as desired. It is very important to take psyllium with plenty of fluids; each dose should be taken with at least 8 ounces of water. Adequate hydration helps reduce bloating and the risk of bowel obstruction; inadequate hydration can also, in extreme cases, cause choking. As psyllium ferments less than certain other dietary fibers, psyllium may also result in less bloating than certain other dietary fibers (Gunn et al., 2022; Sheer & Alois, 2024), but bloating is nonetheless a potential adverse event of psyllium use.

Many studies do not report on adverse events with psyllium. One meta-analysis from 2000 included safety data from 19 clinical trials with a total of 1,628 patients. Most of these trials were 8 weeks or longer in duration; patients received 10.2 grams of psyllium a day. Many of the participants had hypercholesterolemia. There was no significant difference in the number of people who reported

adverse events in the psyllium group compared to the placebo group. Participants in the psyllium group numerically reported more of certain types of adverse events, though the authors did not state if these differences were significant. For instance, the psyllium group reported more digestive adverse events (24.1% vs. 20.6%) and flatulence (9% vs. 5%). In total, 20 patients, including 14 who received psyllium, reported serious adverse events. Of these, 18 were judged to have no relation to psyllium treatment; 1 of the remaining serious adverse events was in a patient who received psyllium and had hernia surgery, and the relation of the event to the psyllium was judged to be unknown. There were no clinically meaningful effects on vitamin and mineral status identified in a subset of these 19 trials that performed serum and urine vitamin and mineral analyses (Anderson et al., 2020).

Anaphylactic allergies to psyllium have been reported, particularly among individuals whose work environments expose them to significant amounts of psyllium particles in the air (Khalil et al., 2003).

A ConsumerLab report found that several brands of psyllium supplements contained potentially concerning lead levels; individuals may want to confirm their supplement meets safety standards.

Drug interactions:

Overall, psyllium may interact with oral medications if the other medications and psyllium are taken at the same time, as psyllium might decrease absorption of the other drug. Individuals should take oral medications at least two hours before or after a dose of psyllium (Drugs.com)

According to Drugs.com, psyllium is known to interact with 29 drugs; none of the interactions are serious, while 2 are moderate and 27 are minor. The two moderate drug interactions are with lactulose, as the effects of psyllium may make it difficult to assess whether the dosage of lactulose is sufficient, and with the radio tracker fluorodeoxyglucose (F18) as psyllium may impact the diagnostic result of fluorodeoxyglucose (F18) (Drugs.com). Psyllium might lower the absorption and thus the efficacy of tricyclic antidepressants, an anti-seizure medication known as carbamazepine, digoxin, and lithium. As psyllium may lower blood sugar, patients receiving diabetic medication and taking psyllium should speak with their doctor; they may require additional monitoring or dose adjustments to prevent hypoglycemia. Psyllium can also lower cholesterol and may positively interact with bile acid sequestrants (Mount Sinai Health Library).

Many laxatives, including psyllium, are contraindicated for patients with intestinal obstruction disorders or inflammatory bowel disease. Bulk forming laxatives like psyllium are contradicted for patients with intestinal obstruction and for renal dysfunction. This class of laxatives is not recommended for the latter condition because they require consuming at least 8 ounces of fluid per dose, and patients with renal dysfunction may have fluid restrictions (Drugs.com).

Research underway:

There are currently 8 ongoing trials registered on clinicaltrials.org that are testing psyllium. Most are assessing the impacts of psyllium on gut function or health, including on the gut microbiome. No studies are assessing psyllium for use for any type of cognitive enhancement or impairment.

Psyllium is also being used as a placebo or active comparator control for some studies.

Search terms:

Pubmed, Google: psyllium, ispaghula, metamucil

- Safety, cognition, blood suger, blood presure, cholesterol, body weight, colon cancer, ulcerative colitis

Websites visited for psyllium:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- ConsumerLab.com
- Cafepharma

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