



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.

Phosphatidylserine

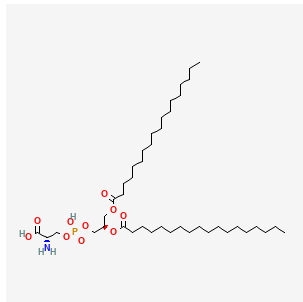
Evidence Summary

Several small studies have indicated a potential benefit of PS for cognition. However, large, rigorous, updated studies of specific formulations of PS are needed both for efficacy and confirmation of safety.

Neuroprotective Benefit: Small trials have found potential benefits of PS, but the results are hard to compare due to formulation and study design differences. Outstanding questions including BBB permeability and bioavailability remain.

Aging and related health concerns: The effects of PS in aging and related health conditions have largely not been studied. There is one study reporting minor increase in mobility in elderly from a combined supplement.

Safety: While PS is thought to be well-tolerated, the safety profile is not thoroughly characterized. Gastrointestinal complaints appear to be one of the more common adverse events.

<p>Availability: in food and/or as a supplement</p>	<p>Dose: The best dose for cognitive effects is not known, but many studies use oral administration of 300 mg daily of PS.</p>	<p>Chemical formula: C₄₂H₈₂NO₁₀P</p>  <p>MW: 792.1 g/mol Source: PubChem</p>
<p>Half-life: Not known in humans. The half-life of PS depends on the tissue in rats. The plasma half-life is thought to be biphasic, with half-lives of 0.85 and 40 minutes; the half-life in brain may be 8 hours.</p>	<p>BBB: Not known.</p>	
<p>Clinical trials: Largest meta-analysis included 962 participants.</p>	<p>Observational studies: Largest observational study found included 68 patients.</p>	

What is it?

Phosphatidylserine (PS) is a class of phospholipids that is available in foods such as soy, white beans, egg yolks, and liver from chicken and beef, though phosphatidylserine is not necessarily readily bioavailable from diet ([VeryWell Mind](#)). PS is also in a variety of supplements. As reviewed by [Leventis & Grinstein 2010](#) and [Kim et al., 2014](#), PS is an important component of plasma membranes, and is especially important and enriched in neuronal membranes. There, PS is involved in a dizzying array of activities, as membrane fluidity and dynamics affects transport, protein function including behavior of membrane receptors and channels, protein signaling, cell-to-cell communication, and more. Under physiological conditions, PS is typically enriched on the cytoplasmic side of the membrane. PS is involved in the activation of a variety of protein signaling pathways, including Akt, protein kinase C (PKC), and Raf-1. In the brain, PS participates in neurotransmission. External PS is also involved in signaling; presence of PS on the outer leaflet of the membrane is an 'eat me' signal, which leads to apoptosis and engulfment of the presenting cell. External PS is involved in activation of blood clotting.



Phospholipids are comprised of one head group and two fatty acid tails. The head group of PS is serine; the fatty acids can vary and can include omega-3 fatty acids such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA), and omega-6 fatty acids such as linoleic acid and arachidonic acid. The fatty acid composition PS can differ significantly depending on whether the PS was synthesized by a plant, fish, or cow. It is therefore difficult to generalize clinical trial results that use very different sources of PS ([European Food Safety Authority, FDA; Kang et al., 2022](#)). Clinical trials also sometimes administer PS as just one of multiple supplements, which adds to the difficulty in parsing the specific effect of PS.

It is also unknown whether PS would be transported intact through the blood and/or able to penetrate the brain ([Kim et al., 2014](#)). In other words, if PS supplementation increases PS concentration in cell membranes in the brain, the effect may occur via its separate components of serine and the fatty acid (DHA or other). However, PS liposomes have been suggested as potential drug delivery vehicles so the blood-brain barrier penetrance of PS itself may depend on the exact formulation ([Ma et al., 2022](#)).

Neuroprotective Benefit: Small trials have found potential benefits of PS, but the results are hard to compare due to formulation and study design differences. Outstanding questions including BBB permeability and bioavailability remain.

Types of evidence:

- 2 meta-analyses and systematic reviews
- Over 20 small clinical trials on various formulations
- 6 reviews
- Numerous preclinical studies for the rationale

Several clinical trials have reported the effects of PS supplementation, usually up to 6 months duration. In theory, PS supplementation could shift membrane compositions within days. Unfortunately, predominantly small and variable pilot studies make it difficult to draw firm conclusions.

The brain's composition of PS is largely constant throughout life although slight changes in varying directions have been reported in Alzheimer's disease (AD) ([Cunnane et al., 2012](#)), Parkinson's disease (PD) ([Fabelo et al., 2011](#)), schizophrenia ([Schmitt et al., 2004](#)), and aging ([Strommel et al., 1989](#)). However, most PS in the brain is synthesized locally ([Kim et al., 2014](#)) and it is not clear whether PS



supplementation will raise brain levels. Although one mouse study does support the idea ([Ohkubo & Tanaka, 2010](#)), this may have been an indirect effect of the DHA in the PS. The local synthesis of PS is most easily done from DHA-phospholipids (phosphatidylcholine and phosphatidylethanolamine) in cell membranes so DHA supplementation may increase PS levels in neuronal membranes ([Kim et al., 2014](#)).

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

Few studies have examined the effects of PS on cognition in healthy adults. A 2011 study examined the effects of soy-derived PS compared to placebo on cognition and mood in young adult men. The 18 participants were randomized to take either 400 mg PS or placebo for 2 weeks, then received cognitive assessments; they then were switched to the other study arm for 2 weeks and repeated the testing. The authors reported that the PS supplementation period was associated with improved cognitive performance as measured by serial subtraction test compared to placebo ([Parker et al., 2011](#)).

Human research to suggest benefits to patients with dementia:

Multiple small clinical trials have reported that PS, particularly PS from bovine brain cortex, could improve cognitive function and sometimes depression in elderly people with dementia, with mild cognitive impairment, or age-associated memory impairment. A 2022 systemic review and meta-analysis assessed results from 5 randomized controlled trials (n=783) and four pre-post studies (n=178), including one open-label extension of one of the aforementioned RCTs. The studies ranged in dose from 100 mg – 300 mg of PS a day, with most using 300 mg a day; the studies utilized PS from bovine brain cortex, soybeans, and marine sources. Four of the five RCTs used PS from bovine brain cortex, and three of the total nine studies administered PS and DHA + EPA as well. The duration also varied from 6 weeks to 6 months. The measurements of cognition were also different between studies. The meta-analysis of the 5 RCTs found that the standard mean difference of the effect of PS vs. placebo on cognitive function was statistically significant (SMD=0.22; 95% CI 0.06 to 0.38, p<0.01) ([Kang et al., 2022](#)).

In the largest of the trials included in the meta-analysis, a double-blind trial from Italy, PS-DHA from bovine cortex (300mg/d) reportedly improved memory, learning, motivation, and socialization over 3-6 months in 494 patients ([Cenacchi et al., 1993](#)).

Due to concerns of mad-cow disease, the PS-DHA from bovine cortex is no longer available but alternatives have been generated from marine sources. Their composition is different from the bovine-

cortex supplements but in one randomized double-blind trial and an open-label follow-up ([Vakhapova et al., 2010](#); [Vakhapova et al., 2014](#)), DHA-enriched PS from marine sources (e.g. Vayacog[®]) for 15 weeks improved some but not most aspects of cognitive function in 157 elderly people with memory impairment. The number of patients who were rated as clinically improved was not significantly different despite a positive trend of 37% of treated patients versus 28% control ([Vakhapova et al., 2010](#)). Longer treatment (i.e. 30 weeks instead of 15) did not lead to further improvements in cognitive function.

The following trials were not included in the above meta-analysis. PS derived from soy (PS-soy) has been tested in several clinical trials with varying and unconvincing effects in elderly people with memory complaints. The best designed study reported that PS-soy at 300 or 600 mg/day had no effects over 12 weeks ([Jorissen et al., 2001](#)). A couple uncontrolled studies have reported cognitive benefits ([Richter et al., 2012](#); [Zanotta et al., 2014](#)) but these are unconvincing given that in another randomized trial the placebo and treated groups all improved to the same degree ([Kato-Kataoka et al., 2010](#)).

In theory, the effects of DHA-enriched PS could be replicated by DHA/fish-oil given with PS-soy because the molecular components may be separated before reaching the brain. In 6 month RCTs, combined supplements failed to influence cognition or hemodynamics in healthy adults aged 50-70 years with subjective memory deficits ([Jackson et al., 2016](#)) but improved scores on 2 of 4 cognitive assays in high-performing elderly women ([Strike et al., 2016](#)).

[More et al., 2014](#) details the results of two pilot studies using soy-derived 100 mg PS + 80 phosphatidic acid (PA) in older adults. They also discuss historical prospective data of the use of PS in geriatric patients. Their first study was a 3-month RCT comparing PS + PA to placebo in 72 cognitively intact adults 60 to 80 years of age. Their second study was a 2-month RCT of PA + PS vs. placebo in 96 patients with AD. The authors report modest improvements on certain measures of memory in the cognitively intact older adult group taking PS + PA as compared to placebo. They also report some mitigation of decline in daily functioning in patients with AD taking PS + PA as compared to placebo after 2 months. However, it is impossible to parse the effects of PS vs. PA.

There are potentially promising results from some of these trials. However, the difficulty in comparing different formulations of PS as well as the very different measures of cognition used, as well as the small size of many of these trials and the mix of administered lipids make it difficult to confidently state that



there is a positive impact of this phospholipid. Large, rigorous clinical trials using non-bovine brain cortex PS alone are necessary to clearly delineate potential effects of PS itself on cognition.

PS has been suggested to benefit patients with Parkinson's disease (PD) ([Funfgeld et al., 1989](#)), but research into the effects of PS in human patients with PD is sparse.

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

[Ma et al., 2022](#) reviewed phosphatidylserine and its role in neuronal function and dysfunction. PS is particularly enriched in the brain, where it participates in a number of crucially important neuronal tasks. The diversity of these physiological roles means that there are also a number of potential mechanisms through which PS can exert neuroprotective effects.

As a component of the plasma membrane, PS affects the behavior of membrane proteins that are necessary for transport in and out of the cell as well as membrane receptors that are involved in cell-to-cell communication. PS is also part of signaling cascades that can affect cognition in multiple ways. For instance, PS can modulate glutamate NMDA receptors through PKC activation and also by changing the density and/or localization of NMDA receptors ([Ma et al., 2022](#)).

PS is also more directly involved in neurotransmission. Synaptic vesicles contain PS as well, and PS participates in synaptic vesicle docking and fusion, as well as re-uptake of neurotransmitters. PS can affect synaptic efficiency and long-term potentiation (LTP), including through modulating synaptic density ([Ma et al., 2022](#)).

Presence of PS on the external side of the plasma membrane marks a cell as apoptotic and targets that cell for phagocytosis, a process that can be less inflammatory than alternate cell death pathways like necrosis ([Ma et al., 2022](#)). PS may also be involved in clearance of aggregates such as A β plaques as well as cells with tau aggregates by acting as a marker for phagocytosis ([Zhuang et al., 2022](#)). PS is thought to have anti-inflammatory actions, such as decreasing expression of pro-inflammatory cytokines and modulating activation of microglia ([Ma et al., 2022](#)).

However, whether these potential mechanisms are in fact at play in dementia and whether supplemental PS can positively impact disease course is not yet fully understood. For instance, it is not known whether orally or intravenously administered PS actually modulates the membrane properties of



neurons ([Kim et al., 2014](#)). Even the relative levels of PS in disease are a matter of debate. The levels themselves may also not be as important as the localization of the phospholipid.

APOE4 interactions:

Although DHA itself has evidence for interaction with APOE4, little research is available on whether potential PS benefits (whether PS-DHA or other) will vary across E4 carriers vs non-carriers. A couple rodent and small human studies suggest that APOE allele can affect PS composition of cell membranes ([Igbavboa et al., 2002](#), [Fitz et al., 2021](#)) but not all studies agree ([Sharman et al., 2010](#)). As the localization of PS is an important factor, not just absolute levels, it is especially difficult to predict the clinical implications of these findings.

Aging and related health concerns: The effects of PS in aging and related health conditions have largely not been studied. There is one study reporting minor increase in mobility in elderly from a combined supplement.

Types of evidence:

- 1 clinical trial on mobility
- 3 reviews

The rationale for aging biology effects beyond the brain is weak. Changes with age have been investigated with phosphatidylserine asymmetry across peripheral cell membranes (e.g. [Franco et al., 2011](#)) without mention of a loss of PS in cell membranes outside of the brain, perhaps in part due to the relative enrichment of PS in neuronal membranes as compared to other tissues.

As reviewed by [Kaynak et al., 2022](#), PS is thought to play a role in cancer through its actions in immune system regulation and apoptotic signaling. For instance, PS is under investigation as a cancer biomarker, as cancer cells may have different localization of PS across the membrane and therefore allow for differentiation from normal cells. There is also a monoclonal antibody against PS known as bavituximab that is currently in clinical trials as an immune modulator ([NCI](#)). As the localization of PS rather than the expression of PS is thought to be important in cancer, it is not clear if PS supplementation would impact cancer progression.

A combination supplement that includes 70 mg of PS (Efalex active 50+) was reported to modestly improve mobility in high-performing elderly women after 6 months of treatment in a randomized double-blind trial ([Strike et al., 2016](#)). Whether the effect is due to PS is unclear.

Safety: While PS is thought to be well-tolerated, the safety profile is not thoroughly characterized. Gastrointestinal complaints appear to be one of the more common adverse events.

Types of evidence:

- 1 meta-analysis and systematic review
- 1 scientific opinion from a governing body
- 4 clinical trials
- 1 review

Small clinical trials suggest that PS supplements are safe in elderly people with minimal side effects other than slightly reduced blood pressure, whether they are DHA-enriched or derived from soy. Longer studies in larger populations are unavailable, whether observational or randomized. Varied and very small clinical studies suggest possible decrease in cortisol from bovine cortex PS-DHA. Due to concerns for prion disease, PS from bovine cortex is no longer available.

A 2022 meta-analysis of nine clinical trials of various sources of PS reported that participants had withdrawn from the included studies due to events such as dizziness, 'severe psychomotor agitation', itching, and gastrointestinal discomfort including nausea, flatulence, and vomiting. The authors reported that it could not be determined whether these symptoms were due to the intervention, and that there were no major adverse events included in the studies ([Kang et al., 2022](#)).

One of the larger studies included in [Kang et al., 2022](#) was a 2010 RCT of 157 elderly adults with subjective memory complaints. Subjects received either 300 mg of PS + 79mg DHA + EPA (Vayacog) daily or placebo. The trial reported no clinically meaningful differences in lab results or on physical examination. There were more adverse events in the PS-DHA treated group (16 events in 10 participants) as compared to placebo (11 events in 8 participants), and there were far more gastrointestinal complaints in the PS-DHA group than in the placebo group (13 events vs. 2 events). No serious adverse events were reported ([Vakhapova et al., 2010](#)). Resting diastolic blood pressure was decreased after 30 weeks in the open-label extension (3.1 mmHg, $p=0.006$) and a slight weight gain was



reported (0.7 kg, $p=0.015$). A wide variety of biochemical parameters were unchanged (eg. cholesterol, bilirubin, glucose, and others) ([Vakhapova et al., 2011](#)). This formulation is no longer available in the US.

PS-soy, in a handful of small clinical studies in elderly people at doses between 100-600 mg/day, had a good safety profile with no adverse effects ([More et al., 2014](#)). In one open-label trial, systolic and diastolic pressure was decreased ([Richter et al., 2012](#)). Some evidence suggests that PS-soy in exercising people could reduce the cortisol response to overtraining or improve exercise capacity ([Kingsley 2006](#)).

Drug interactions:

There is mixed information as to what, if any, drug interactions PS has. PS may affect cholinergic signaling, and so could interact with anticholinergic drugs such as those used for glaucoma and AD ([WebMD](#)). Some sources also cite potential interactions with anti-inflammatories, antihistamines, and antidepressants. Finally, PS may increase risk of bleeding, and so may interact poorly with anticoagulants, and may be best avoided before surgery ([WebMD](#); [VeryWell Mind](#)).

Research underway:

There are seven ongoing trials that are investigating the effects of phosphatidylserine, whether alone or in combination with other supplements. Three of the trials focus on cognitive function and one examines the efficacy of phosphatidylserine in type 2 diabetes.

[NCT04920305](#) is a randomized, placebo controlled, double-blinded study in 100 cognitively intact adults 60 to 70 years of age. Participants will take either placebo or 600 mg of phosphatidylserine daily for 6 months. The researchers will administer MRI, EEG, and cognitive assessments at baseline and after the end of the 6 month dosing period to assess functional connectivity and change in cognitive function, including working memory. The study was set to begin in 2022; however, it does not appear to have started enrollment as of October 2023.

[NCT05962008](#) is a 12-week randomized, placebo controlled, double-blind study. They plan to enroll 114 healthy adults 35-65 years of age. Subjects will be randomized to one of three groups: placebo, 300 mg daily of omega-3 phosphatidylserine derived from herring roe, and 300 mg daily of phosphatidylserine



from soybean. The outcome measures are changes in different aspects of cognitive function from baseline to the end of the trial.

[NCT05520424](#) is an open label trial that focuses on the effects of a supplement that contains phosphatidylserine, along with other compounds including curcumin, ginseng, epigallocatechin, vitamins B6, and B12. They aim to enroll 40 participants 30 to 60 years of age who will all take the supplement for 30 days. The outcome measures include self-reported perceptions of mental health and stress, as well as changes in cognitive function and blood biomarkers such as HbA1c and IL-6 over the course of the study. The study is sponsored by the manufacturer, Parable.

[NCT04557228](#) aims to assess how phosphatidylserine impacts vascular function and insulin-stimulated blood flow in patients with Type 2 diabetes. The double-blinded study aims to enroll 34 subjects who will be randomized to either placebo or 900 mg daily of phosphatidylserine. The study will last for 4 weeks. The outcome measures include change in insulin-stimulated blood flow and change in vascular function between baseline and end of the trial.

Search terms:

Pubmed, Google: phosphatidylserine

- Dementia, Alzheimer's, Parkinson's disease, blood-brain barrier, observational, cancer, diabetes, APOE4

Websites visited for phosphatidylserine

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Examine.com](https://examine.com)
- [Drugs.com](https://drugs.com)
- [WebMD.com](https://webmd.com)
- [PubChem](https://pubchem.ncbi.nlm.nih.gov)
- [DrugBank.ca](https://drugbank.ca)
- [ConsumerLab.com](https://consumerlab.com)



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