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.

Plasmalogen

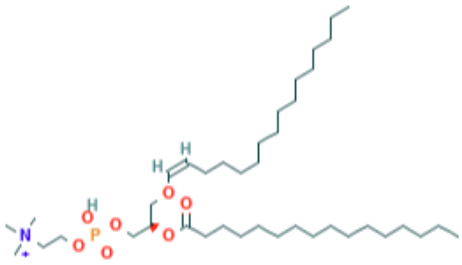
Evidence Summary

Evidence suggests that plasmalogens decrease in brain tissue of Alzheimer's patients and reduced serum levels of plasmalogens increase risk for Alzheimer's, though one clinical study of plasmalogen supplementation suggests mixed results.

Neuroprotective Benefit: There is a biological rationale that plasmalogens may be beneficial for Alzheimer's or cognitive aging, but the type and dosage need to be determined.

Aging and related health concerns: There are some correlations with serum plasmalogen levels and cardiovascular outcomes, though it is unclear whether plasmalogen supplementation would be useful.

Safety: One study reported no differences in safety between scallop-derived plasmalogens and placebo in Alzheimer's patients, but further studies of specific plasmalogens are warranted.

Availability: Available online (NeuroREGAIN), the supplement presumably used in the AD trial.	**Dose:** 1mg/day purified from scallops from the AD trial	**Chemical formula:** $C_{40}H_{81}NO_7P$ **MW:** 719.062g/mol Source: Pubchem 
Half life: Days (for plasmalogens derived from PPI-1011, a plasmalogen precursor)	**BBB:** Penetrant in animals (for PPI-1011)	
Clinical trials: One in Alzheimer's disease	**Observational studies:** 0	

What is it?

Plasmalogens (Pls) are glycerophospholipids containing a vinyl ether-linked fatty alcohol at the sn-1 position of the glycerol backbone, an ester-linked fatty acid at the sn-2 position, and a phosphatidyl choline or ethanolamine at the sn-3 position. They constitute 18%-20% of the total phospholipids in cell membranes. They are predominantly abundant in the brain, retina, leukocytes, sperm, heart and skeletal muscle in mammals. Most Pls are phosphatidyl ethanolamine Pls (PlsPE) or phosphatidyl choline Pls (PlsC). PlsPEs are generally more abundant than PlsCs, except in the heart and skeletal muscle tissue (Fujino et al, 2017). PlsPEs make up about 30 mol% of the total phospholipid and 90 mol% of the ethanolamine phospholipids in the neuronal membrane (Grimm et al, 2011).

Pls are synthesized in the peroxisome, and Pls concentration declines with age. The reduction of plasmalogens with age could be the result of decreased peroxisome function or an increase in the activity of the enzyme that degrades plasmalogens, Pls-specific phospholipase A_2 (PlsPE-PLA_2) (Goodenowe et al, 2007).

An example of plasmalogen nomenclature is PlsPE(18:0-22:6), where PE is the moiety at the sn-3 position, 18:0 the moiety at the sn-1 position, and 22:6 the moiety at the sn-2 position. 18 and 22 indicate the number of carbons on the side chain while 0 and 6 indicates the number of double bonds.

Different Pls are enriched in the cerebral white and grey matter. White matter Pls included 18:1, 20:1, and 22:4 while grey matter Pls include 20:4, 22:4, 20:4, and 22:6 (docosahexaenoic acid – DHA) (Lizard

et al, 2012). Since the white matter is primarly composed of myelin, which possesses a compact membrane, white matter plasmalogens contain more saturated side chains. In contrast, polyunsaturated plasmalogen side chains are enriched in grey matter since they assist in signal transduction.

Plasmalogens may act through multiple mechanisms. They are part of the plasma membrane, making it more fluid and thereby increasing cellular signaling and improving membrane fusion. In plasmalogen rich portions of the membrane, APP is reported to be processed by alpha-secretase rather than gamma-secretase (the secretase that processes Aβ aggregates). They are also reported to be involved in cholesterol efflux. Finally, since they have a vinyl ether bond at sn-1, they may act as antioxidants.

Neuroprotective Benefit: There is a biological rationale that plasmalogens may be beneficial for Alzheimer's or cognitive aging, but the type and dosage need to be determined.

Types of evidence:

- 1 clinical trial in patients with mild cognitive impairment (MCI) and mild Alzheimer's
- Multiple histopathology and serum biomarker studies
- Two preclinical animal studies

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

None

Human research to suggest benefits to patients with dementia

In a 24-week study in 328 patients with MCI or mild Alzheimer's, 1mg/day of scallop-derived Pls had no effect on the primary cognitive outcome (MMSE) or on memory. In a subgroup analysis, Pls had no effect on MMSE scores in mild Alzheimer's patients, but there was a trend toward improved memory (p=0.078) which was significant in women (p=0.02) but not men and in patients under the age of 77 (p=0.03) but not older patients. No information was reported for patients with MCI. Pls supplementation increased plasma PlsPEs in the treatment group but not erythrocyte PlsPE levels (Fujino et al, 2017).

Histopathological studies

Ginsberg et al (1995) reported a 31% reduction in the PlsPE/phosphatidyl ethanolamine (PE) ratio in post-mortem tissue in Alzheimer's patients with no reduction in Parkinson's or Huntington's patients. The reduction in PlsPE were confirmed by a separate group (Farooqui et al, 1997). Guan et al (1999) reported a decrease in phospholipid concentrations in the frontal cortex and hippocampus (but not white matter) of Alzheimer's patients that was specifically due to a reduction in PlsPEs (50% in frontal cortex, 31% in hippocampus). Wood et al (2015) reported a decrease of certain PlsPE species (40:6, 36:4, 38:4) in the gray matter, but not the white matter, of young and old dementia patients but not MCI patients.

On the other hand, one study reported an increase in PlsPE in post-mortem Alzheimer's tissue. The authors speculate that the difference could be due to the method of measuring Pls. They use ^{31}P-NMR in post-mortem tissue while other studies used high-pressure liquid chromatography or high-performance thin layer chromatography – methods that require substantial pre-processing and do not directly measure Pls (Pettegrew et al, 2001).

Using a more sensitive method to measure phospholipids, Han et al (2001) also reported a decrease in PlsPE content up to 30% in the frontal, parietal, and temporal (but not cerebellar) cortices in patients with moderate Alzheimer's disease that correlated with disease severity. They also reported a decrease in PlsPE content up to 40% in the white matter of the frontal, parietal, and temporal cortices as well as the cerebellum at the earliest stages of the disease which did not decline further with disease severity. The plasmalogen species with the greatest decline in the grey matter included Pls(18:1-18:1)/(18:0-18:2) and Pls(18:0-22:6) while the species with the greatest decline in the white matter was Pls(18:1-18:1).

Rothhaar et al (2012) reported that PlsPC levels were reduced in post-mortem Alzheimer's frontal cortex with the greatest reduction in PlsPC(18:1-18:1) (~51% reduction) while there was no significant reduction in PlsPE. However, previous studies by the same group reported significant reductions in PlsPE and PlsPC in post-mortem Alzheimer's tissue (Grimm et al, 2011; Grimm et al, 2011).

Serum biomarker studies

Goodenowe et al (2007) reported that serum levels of Pls were reduced in clinically diagnosed Alzheimer's patients, that the reduction correlated with disease severity, and reduction of Pls were greater than free DHA (white matter PlsPE – 16:0-18:1, 18:0-18:1, 16:0-18:2, 18:0-18:2; grey matter PlsPE – 16:0-20:4, 18:0-20:4, 16:0-22:6, 18:0—22:6). Serum PlsPE(16:0-22:6) levels were also reduced in post-

mortem confirmed Alzheimer's patients. Using a linear extrapolation of plasmalogen levels, they estimated that plasmalogens began to decrease up to 7 years before the onset of clinical diagnosis. Yamashita et al (2016) reported a reduction in multiple PlsPE in the serum of Alzheimer's patients compared to controls, while Wood et al (2010) reported that in patients with PlsPE(DHA) levels <75% of normal controls experience cognitive decline over one year while patients with the highest levels of PlsPE(DHA) remained stable. Oma et al (2012) also found that the PlsPE/sphingomyelin ratio was reduced in Alzheimer's patients.

Goodenowe and Senanayake (2019) reported that for each standard deviation increase in the serum plasmalogen biosynthesis value (PBV – a measure of plasmalogens in the blood) was associated with a reduced risk of dementia (OR = 0.607, $p=3.3x10^{-6}$), improvement on five cognitive domains, and found that PBV was an independent of ApoE genotype.

Interestingly, in patients with familial Alzheimer's disease, serum Pls were increased in asymptomatic mutation carriers but were inversely correlated with CSF tau and amyloid PET (suggesting an inverse correlation with disease progression). The authors speculate this may be a compensatory mechanism, increasing levels of Pls to cope with increased oxidative stress, in the early stages of the disease (Chatterjee et al, 2016).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In an animal model of systemic LPS injection, Pls co-injected with LPS over 7 days reduced the expression of inflammatory microglia, prevented the LPS-induced accumulation of AB, and prevented the reduction of PlsPE (Katafuchi et al, 2012). In an Alzheimer's animal model, 15-month treatment with scallop-derived Pls reduced the expression of markers of inflammation (Iba-1) and the expression of a protein thought to be involved with inflammation and apoptosis (PKCδ). PKCδ was also reported to be increased in post-mortem tissue from Alzheimer's patients (Sejimo et al, 2018).

In cell culture experiments, Rothhaar et al (2012) reported that PlsPC and PlsPE reduced gamma-secretase activity compared to non-Pls PC/PE, and in cell membranes isolated from post-mortem Alzheimer's tissue, PlsPC also reduced gamma-secretase activity.

PPI-1011
PPI-1011 is a synthetic plasmalogen precursor with a palmityl group at the sn-1 position, DHA at the sn-2 position, and lipoic acid at the sn-3 position. In a primate Parkinson's model (MPTP) comparing PPI-1011 to DHA, PPI-1011 (50mg/kg) reduced L-dopa-induced dyskinesia while retaining the anti-Parkinson's

effect of L-dopa after 2 days while DHA improved outcomes after 10 days. Only DHA increased plasma DHA levels while both drugs increased the levels of PlsPE(DHA) (Gregorie et al, 2015).

In a mouse MPTP model, PPI-1011 increased serum PlsPE and non-significantly increased brain PlsPE. However, PPI-1011 treatment protected against striatal dopamine reduction and striatal dopamine neuronal loss (Miville-Godbout et al, 2016). In an isotope labeling study of PPI-1011 in rabbits, after administration of 200mg/kg of labeled PPI-1011, labeled PlsPE(DHA) was found in brain tissue, suggesting it can cross the blood brain barrier (Wood et al, 2011).

APOE4

One study, Goodenowe and Senanayake (2019), found that plasmalogen levels and ApoE4 are independently associated with the risk of Alzheimer's disease, but it is not known whether efficacy of plasmalogen supplements would be different in ApoE4 individuals.

Aging and related health concerns: There are some correlations with serum plasmalogen levels and cardiovascular outcomes, though it is unclear whether plasmalogen supplementation would be useful.

Types of evidence:

- 3 serum biomarker studies
- 3 preclinical studies

Inverse associations between serum plasmalogen levels and cardiometabolic diseases such as obesity, T2DM, and cardiovascular disease have been reported (Paul et al, 2019). For instance, in a study of 265 patients with peripheral artery disease, after measuring 332 different lipid species, higher levels of PlsPC species conferred the greatest reduced risk of future myocardial infarction after 23 months (HR = 0.28; 95%CI 0.14-0.56 per SD increase) (Moxon et al, 2017). In a cross-sectional study of 50 patients with coronary artery disease (CAD), lower levels of PlsPC and PlsPE species were associated with significant coronary stenosis and multiple risk factors of CAD, such as BMI, number of lesions, dyslipidemia. Lower levels of PlsPC and PlsPE were more associated with significant coronary stenosis than other risk factors, such as HDL-c and adiponectin (Nishimukai et al, 2014). PlsPC (but not PlsPE) was also inversely associated with patients with stable CAD compared to controls (Meikle et al, 2011).

In preclinical models of heart failure, heart plasmalogen content was reduced in a model of small hearts due to depressed PI3K signaling (dnPI3K) and cardiomyopathy, but not in a physiological cardiac hypertrophy model. Treatment with a plasmalogen precursor, batyl alcohol (BA), for 16 weeks did not

reverse the dnPI3K and cardiomyopathy phenotypes. BA is a precursor to 18:0 plasmalogens, and the authors speculate that the lack of beneficial effect was due to the fact that BA did not increase other plasmalogen species, which were also reduced (Tham et al, 2018). On the other hand, BA treatment over 12 weeks reduced plaque size by ~70% in an animal model of atherosclerosis (ApoE-/- w/HFD). Lipid measurements showed the BA increased the levels of triglycerides and reduced levels of HDL-c in control mice while improving fasting glucose levels in atherosclerosis mice (Rasmiena et al, 2015). *In vitro* supplementation of plasmalogens also improved survival in human endothelial cells subjected to hypoxia (Zoeller et al, 2002).

Safety: One study reported no differences in safety between scallop-derived plasmalogens and placebo in Alzheimer's patients, but further studies of specific plasmalogens are warranted.

Types of evidence:

- One RCT

One RCT of 328 patients with MCI or mild Alzheimer's disease reported no differences in side effects between 1mg/day of scallop-derived plasmalogens and placebo over 24 weeks (Fujino et al, 2017). However, longer studies at larger doses and studies with different plasmalogen species or manufacturing procedures have not been completed.

Drug interactions:
Drug interactions are currently unknown; however, DHA, one component of some plasmalogen species, may interact with blood pressure medications (it may lower blood pressure) and anti-coagulants.

Sources and dosing:
Plasmalogens are currently sold as a supplement online (NeuroREGAIN). Presumably this is the product used in the Alzheimer's trial. The trial used 1mg/day.

In addition to scallops, plasmalogens are also found in shark liver oil, krill oil, and other marine food (Paul et al, 2019).

Research underway:
A phase 1 safety/PK study of PPI-1011, funded by the Alzheimer's Association, is set to begin early this year.

Search terms:
Plasmalogen + Alzheimer, dementia, cardiovascular, aging

Websites:
Clinicaltrials.gov
Pubmed