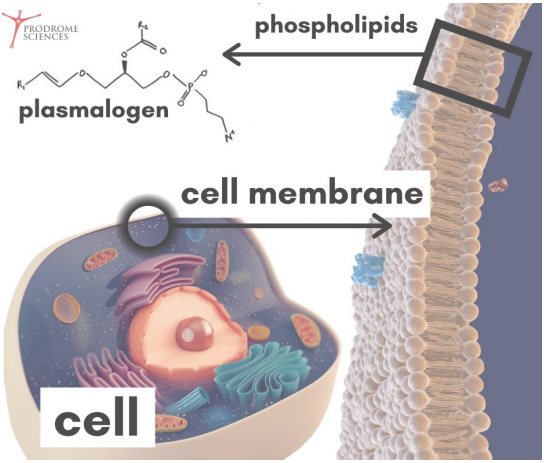
PLASMALOGEN DEFICIENCY, DEMENTIA, AND DEATH

PART 1

What are Plasmalogens?

Plasmalogens are a special type of phospholipid. They are found in high concentrations in the brain, heart, lungs, kidneys, and eyes. Plasmalogens are not a trace nutrient, instead they build a large part of the brain, as much as 20% of the dry weight.



Decades of data show that:

1. Low plasmalogen levels have severe health effects.
2. Plasmalogen supplementation has positive health effects.

Plasmalogens act as a reservoir for important fatty acids[1]. including oleic acid, arachidonic acid, and docosahexaenoic acid (DHA). Plasmalogens are anti-inflammatory, are powerful antioxidants, are a critical part of cell membranes, maintain optimal brain function, and are a major structural part of lipoproteins, myelin, and synaptic membranes[2].

Plasmalogen levels in the brain increase up to 30 to 40 years of age and then significantly decrease by around 70 years of age[3]. There are no adequate food sources it can be derived from. The body makes plasmalogens in the peroxisomes of cells (the majority are made in the liver). The body's ability to make plasmalogens becomes impaired as peroxisome function is compromised with age and plasmalogens are degraded from inflammation and oxidative stress.

PART 2

Why are Low Levels of Plasmalogens so Bad?

There is no question that plasmalogens are important for health. But what about having low levels of plasmalogens – just how bad can it be? I have made a lot of graphs in my career and only one graph has actually scared me: the relationship between blood plasmalogen levels and death (*Figure 1*).

Plasmalogens and death.

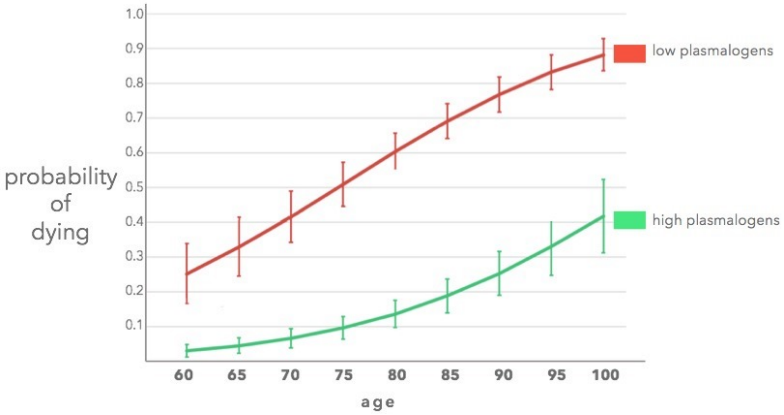


Figure 1. Probability of dying in 5.3 years
Data from the Rush University Memory and Aging Project. Final dataset: 1262 participants, participants still living since last clinical visit = 896, participants deceased since last visit = 862. Average age at enrolment = 81. Low plasmalogens = 5th percentile +/- 95% CI. High plasmalogens = 95th percentile +/- 95% CI.

Data from the Rush University Memory and Aging Project showed that a 95 year old with high plasmalogen levels had the same chance of dying in five years as a 65 year old with low plasmalogen levels. A 95 year old with high levels had an almost 70 percent chance of living to their 100th birthday whereas a person the same age with low plasmalogen levels had a less than 20 percent chance of living to their 100th birthday. These results were shocking.

PART 3

Plasmalogens & Neurodegeneration

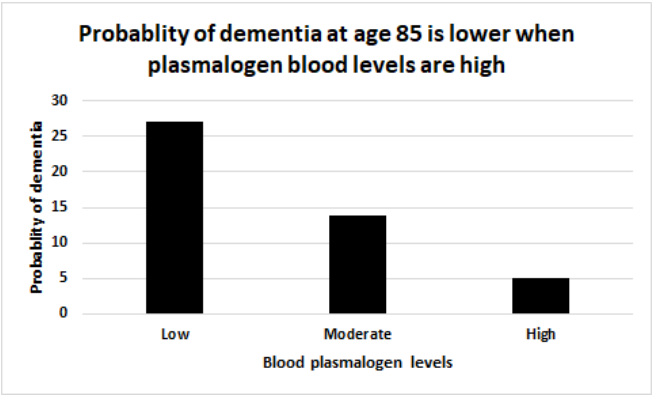
Plasmalogens are involved in several diseases. I have studied them since 2006 when I first discovered and hypothesized[4] about the role of plasmalogens in the cause of dementia. Since then, research evidence has expanded to show that plasmalogens are part of the root cause of neurodegeneration that leads to Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. Most published data available is for plasmalogens and dementia. Plasmalogen deficiency is associated with cognitive impairment and Alzheimer's disease[5]. The severity of dementia correlates with the severity of plasmalogen deficiency, irrespective of APOE allele status which is the second biggest risk factor for Alzheimer's disease after[6].

People with dementia have low plasmalogen levels.

- Levels are significantly lower in people with all stages of dementia.
- The lower the plasmalogen levels, the more severe the disease.
- Levels decrease years before any clinical symptoms.

Plasmalogens are a stronger risk factor for dementia than genetics.

- The presence of an *APOE* e4 allele is a genetic risk factor for dementia/ Alzheimer's disease.
- This genetic risk is modified by the plasmalogen level of that person.
- E4 carriers with high plasmalogen levels do not have an increased risk for dementia.



PART 4

Plasmalogens and the cause of Diseases.

Why do we get low levels of plasmalogens? The body makes a lot of plasmalogens and consumes a lot.
Plasmalogen deficiency occurs when the body can no longer make as much as it consumes. This can happen due to increased oxidative stress which degrades plasmalogens[7] or decreased biosynthesis caused by aging and chronic exposure to xenobiotics[8].

What happens when there are not enough plasmalogens in the body?
Plasmalogens have both structural and functional roles in the brain. Plasmalogen deficiency leads to cell membrane changes in structure, geometry, and function as the body is forced to substitute other molecules such as phosphatidylethanolamines[9] in place of plasmalogens. This leads to cellular signaling abnormalities and neurotransmission deficits as well as lowered antioxidant defences[10].

Inflammation can lead to a vicious cycle where oxidative stress degrades plasmalogens which further reduces the anti-inflammatory and antioxidative capacity[11] of the tissues ultimately leading to clinical symptoms of disease.

Alzheimer's disease.
Alzheimer's disease results from neurodegeneration of neurons responsible for cognition: cholinergic neurons. Cholinergic neurons are especially sensitive to decreased membrane fusion activity caused by plasmalogen deficiency because, unlike other neurons, membrane fusion is necessary for both neurotransmitter release and re-uptake. Reduced membrane fusion reduces neurotransmission which reduces cognition.

Parkinson's disease.
Parkinson's disease results from neurodegeneration of neurons responsible for fine motor control: dopaminergic neurons. The direct cause of Parkinson's is unknown, but some environmental neurotoxins selectively target dopaminergic neurons and cause Parkinson's in animals. Plasmalogen deficiency increases susceptibility to neurotoxins.

Multiple sclerosis.

Multiple sclerosis results from neurodegeneration of cells that insulate neurons: myelin or oligodendrocytes. Myelin has the highest concentration of plasmalogens in the whole body. When immune cells are activated to clean up a mess (inflammation), part of the myelin can be damaged and extra plasmalogens are needed to repair the cells before they die. If cells cannot be repaired before they die, the debris creates even more inflammation and degeneration. High levels of plasmalogens prevents demyelination by improving remyelination.

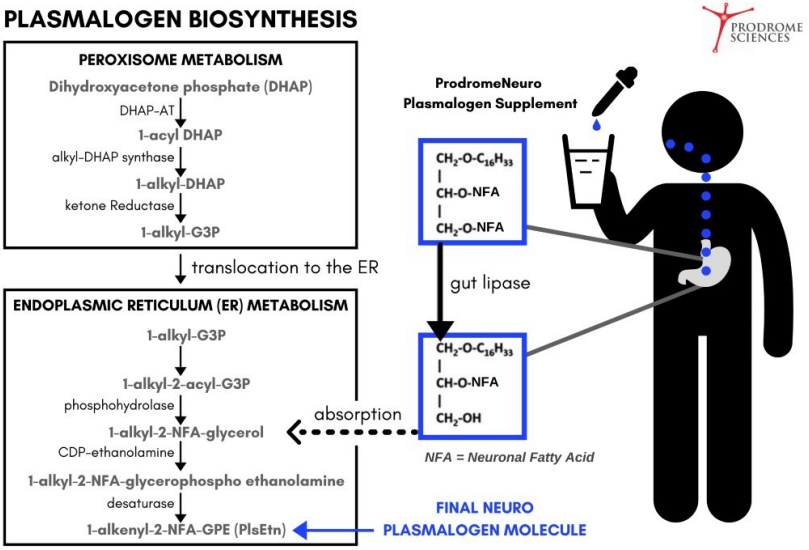
Plasmalogens to prevent disease.

Plasmalogens prevent neurodegeneration in animal models; the majority of the publications are for Parkinson's disease. In a mouse model of Parkinson's disease, an oral dose of plasmalogen at 50mg/kg was fully neuroprotective[12].

PART 5

Scientifically Designed Plasmalogen Supplement

After years of extensive research I designed plasmalogen supplements that function as a plasmalogen precursor, that survives the gut and is then converted into the target plasmalogen molecule independent of peroxisomal function.



To get the right kind of plasmalogen into the body, I designed and patented three different types of plasmalogen precursors that could be converted to plasmalogens in the human body. At Prodrome Sciences, my focus became making a plasmalogen precursor supplement that could effectively restore plasmalogen levels. ProdromeNeuro and ProdromeGlia plasmalogen oil molecules are supplements designed from my original plasmalogen precursor patents. The most important aspect in plasmalogen precursor technology was the discovery that all plasmalogens were not created equal. You need to be able to target specific plasmalogens involved in specific neurological functions. The most important molecule that is needed to supplement and enhance for cognition is the DHA containing plasmalogens. These are the ones associated with decreased cognition in the human brain and these are the types of plasmalogens ProdromeNeuro is designed to

deliver. ProdromeGlia is designed to specifically go into the white matter and act as a protective sheath for the neurons in your brain.

While we continue to advance research on plasmalogens to answer important questions about the use in disease management, one thing is clear today: plasmalogens are an essential brain nutrient you do not want to be low on. My scientifically designed, natural plasmalogen supplement ensures there is an adequate amount of plasmalogens in the blood supply for health.

ABOUT DR DAYAN GOODENOWE PHD

Dr. Goodenowe's research into the biochemical mechanisms of disease started in 1990. His curiosity about the biochemistry of life is as insatiable today as it was 30 years ago. In those 30 years, Dr. Goodenowe invented and developed advanced diagnostic and bioinformatic technologies, designed and manufactured novel and natural biochemical precursors, and identified biochemical prodromes of numerous diseases including Alzheimer's disease and dementia, Parkinson's disease, multiple sclerosis, stroke, autism, amyotrophic lateral sclerosis (ALS), multiple system atrophy, schizophrenia, bipolar disorder, depression, and cancers of the colon, pancreas, ovary, breast, lung, kidney, esophagus, liver, stomach, and endometria. Dr. Goodenowe is going beyond the diagnosis of disease and has set his sights on figuring out how long the human body can maintain the physical and biological functions of life.

Dr. Dayan Goodenowe
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Notes

[1] Han X. (2005). Lipid alterations in the earliest clinically recognizable stage of Alzheimer's disease: implication of the role of lipids in the pathogenesis of Alzheimer's disease. *Current Alzheimer research*, *2*(1), 65–77. https://doi.org/10.2174/1567205052772786

[2] Senanayake, V., & Goodenowe, D. B. (2019). Plasmalogen deficiency and neuropathology in Alzheimer's disease: Causation or coincidence?. *Alzheimer's & dementia (New York, N. Y.)*, *5*, 524–532. https://doi.org/10.1016/j.trci.2019.08.003

[3] Rouser, G., & Yamamoto, A. (1968). Curvilinear regression course of human brain lipid composition changes with age. *Lipids*, *3*(3), 284–287. https://doi.org/10.1007/BF02531202

[4] Goodenowe, D. B., Cook, L. L., Liu, J., Lu, Y., Jayasinghe, D. A., Ahiahonu, P. W., Heath, D., Yamazaki, Y., Flax, J., Krenitsky, K. F., Sparks, D. L., Lerner, A., Friedland, R. P., Kudo, T., Kamino, K., Morihara, T., Takeda, M., & Wood, P. L. (2007). Peripheral ethanolamine plasmalogen deficiency: a logical causative factor in Alzheimer's disease and dementia. *Journal of lipid research*, *48*(11), 2485–2498. https://doi.org/10.1194/jlr.P700023-JLR200

[5] Senanayake, V., & Goodenowe, D. B. (2019). Plasmalogen deficiency and neuropathology in Alzheimer's disease: Causation or coincidence?. *Alzheimer's & dementia (New York, N. Y.)*, *5*, 524–532. https://doi.org/10.1016/j.trci.2019.08.003

[6] Goodenowe, D. B., & Senanayake, V. (2019). Relation of Serum Plasmalogens and *APOE* Genotype to Cognition and Dementia in Older Persons in a Cross-Sectional Study. *Brain sciences*, *9*(4), 92. https://doi.org/10.3390/brainsci9040092

[7] Jenkins, C. M., Yang, K., Liu, G., Moon, S. H., Dilthey, B. G., & Gross, R. W. (2018). Cytochrome *c* is an oxidative stress-activated plasmalogenase that cleaves plasmenylcholine and plasmenylethanolamine at the *sn*-1 vinyl ether linkage. *The Journal of biological chemistry*, *293*(22), 8693–8709. https://doi.org/10.1074/jbc.RA117.001629

[8] Terlecky, S. R., Koepke, J. I., & Walton, P. A. (2006). Peroxisomes and aging. *Biochimica et biophysica acta*, *1763*(12), 1749–1754. https://doi.org/10.1016/j.bbamcr.2006.08.017

[9] Senanayake, V., & Goodenowe, D. B. (2019). Plasmalogen deficiency and neuropathology in Alzheimer's disease: Causation or coincidence?. *Alzheimer's & dementia (New York, N. Y.)*, *5*, 524–532. https://doi.org/10.1016/j.trci.2019.08.003

[10] Braverman, N. E., & Moser, A. B. (2012). Functions of plasmalogen lipids in health and disease. *Biochimica et biophysica acta*, *1822*(9), 1442–1452. https://doi.org/10.1016/j.bbadis.2012.05.008

[11] Su, X. Q., Wang, J., & Sinclair, A. J. (2019). Plasmalogens and Alzheimer's disease: a review. *Lipids in health and disease*, *18*(1), 100. https://doi.org/10.1186/s12944-019-1044-1

[12] Miville-Godbout, E., Bourque, M., Morissette, M., Al-Sweidi, S., Smith, T., Mochizuki, A., Senanayake, V., Jayasinghe, D., Wang, L., Goodenowe, D., & Di Paolo, T. (2016). Plasmalogen Augmentation Reverses Striatal Dopamine Loss in MPTP Mice. *PloS one*, *11*(3), e0151020. https://doi.org/10.1371/journal.pone.0151020