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.

Phosphatidylcholine and Lecithin

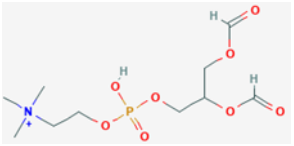
Evidence Summary

Adequate dietary consumption is associated with lower morbidity and mortality with aging, especially in relation to liver health. It is safest when derived from heathy food sources like eggs and soy.

Neuroprotective Benefit: RCTs report no substantial benefit in dementia patients, though adequate dietary intake is associated with lower dementia risk. Altered phosphatidylcholine levels in biofluids may serve as biomarkers of cognitive decline.

Aging and related health concerns: Higher circulating polyunsaturated phosphatidylcholines are associated with healthspan and lower mortality, which may reflect dietary choices. Adequate choline consumption may help protect against liver disease.

Safety: Phosphatidylcholine is widely consumed as part of a normal diet, and aside from mild gastrointestinal events, supplementation is generally well-tolerated. Unlike some other forms of choline, it is not associated with elevations in TMAO.

Availability: OTC	**Dose**: No clinically therapeutic doses. Essential phospholipids for hepatoprotection have been used at 1.8 g/day orally, in clinical studies.	**Lecithin phosphatidylcholine(1+)** **Chemical formula:** $C_{10}H_{21}NO_8P+$ **MW**: 314.25 g/mol  Source: PubChem
Half-life: Varies with formulation	**BBB**: Penetrant	
Clinical trials: Phosphatidylcholine/lecithin has been tested in trials for dementia. Delayed-release lecithin has been tested for ulcerative colitis. Essential phospholipids have been tested for fatty liver disease.	**Observational studies**: Phosphatidylcholine intake has been associated with reduced risk for dementia, as well as mixed risk for mortality, diabetes, and cardiovascular disease, in different populations.	

What is it?

Phosphatidylcholine is a major type of phospholipid and a primary component of cell membranes (phospholipids are lipids with a phosphate head). Supplements are often derived from egg yolk or soybeans. Phosphatidylcholine is a major component of lecithin, a yellow-brown fatty substance found in egg yolk, organ meats, nuts, and spinach. Although lecithin contains substances other than phosphatidylcholine, the terms are sometimes used interchangeably in medical literature. Phosphatidylcholine supplements are well-absorbed through the gut [1].

Neuroprotective Benefit: RCTs report no substantial benefit in dementia patients, though adequate dietary intake is associated with lower dementia risk. Altered phosphatidylcholine levels in biofluids may serve as biomarkers of cognitive decline.

Types of evidence:

- 1 meta-analysis of RCTs with lecithin for treatment but not prevention of cognitive decline
- 1 cohort with internal replication that depletion of some forms predicts risk of dementia
- 2 observational studies associating dietary phosphatidylcholine intake with dementia risk

- 1 RCT testing egg yolk-derived phosphatidylcholine for cognition in healthy older adults
- 8 studies examining biofluid phosphatidylcholine species as AD biomarkers

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

Choline is an essential nutrient that is a precursor for the formation of both phosphatidylcholine, a major component of neuronal cell membranes, and the neurotransmitter acetylcholine [2]. The cholinergic system is one of the first brain systems to be impacted by Alzheimer's disease (AD), resulting in a loss of cholinergic tone. In order to compensate, choline may be diverted toward the production of acetylcholine at the expense of phosphatidylcholine, leading to impairments in cell membrane integrity and function. As a result, adequate choline intake is considered important for the maintenance of cognitive function.
Dietary choline and phosphatidylcholine intake has been associated with lower risk of dementia in observational studies. An analysis of 3,224 participants from the Framingham Heart Study found that choline intake had a nonlinear relationship with dementia risk [3]. Low choline intake, as defined as ≤219 mg/d was associated with higher risk for incident dementia, while low intake defined as ≤215 mg/d, was associated with higher risk for AD, relative to medium choline intake (defined as between 220 and 516 mg/d, and between 216 and 552 mg/d, respectively). Similarly, as a subset of choline intake, phosphatidylcholine was also associated with lower risk for incident dementia and AD. There was a non-significant trend toward increased dementia risk with the highest intake, but the sample size of this group was small. In the population-based Kuopio Ischaemic Heart Disease Risk Factor Study including 2,497 Finnish men, those in the highest quartile of phosphatidylcholine intake (>222 mg/d) had a 28% (95% Confidence Interval [CI] 1 to 48%) lower risk of incident dementia relative to those in the lowest quartile (<144 mg/d) [4]. For incident AD diagnosis, each 50 mg/d higher phosphatidylcholine intake was associated with a Hazard Ratio (HR) of 0.90 (95% CI 0.81 to 1.00). Higher choline and phosphatidylcholine intake was also associated with better performance on cognitive tests involving frontal and temporal lobe function. Phosphatidylcholine intake was associated with better performance on the Trail Making Test A, a measure of cognitive processing speed, the Verbal Fluency Test, and the Russell–s adaptation of the Visual Reproduction Test. These associations were not affected by ApoE4 status.

In a company-sponsored RCT in healthy middle-aged and older Japanese adults (ages 60-80) (n=41), supplementation with egg yolk-derived choline (300 mg/day) for 12 weeks was associated with better

verbal memory scores and verbal memory test-correct hits at six and 12 weeks, relative to baseline [5]. However, Cognitrax processing speed scores, symbol digit coding testing correct responses, and SF-36 physical quality of life summary scores were lower compared to the placebo group at 6 weeks, and not significantly different at 12 weeks. This suggests that phosphatidylcholine-enriched supplements may modestly impact some cognitive parameters related to the cholinergic system without enhancing global cognition.

Phosphatidylcholine species have been identified in metabolite panels of fluid biomarkers as indicators of cognitive decline, however, there is a high degree of heterogeneity across studies [6]. These species are a reflection of both dietary sources of choline as well as alterations in lipid metabolism. Since phosphatidylcholine is also a major component of neuronal cell membranes, levels of cerebrospinal fluid (CSF) phosphatidylcholines and related lipids could be an indication of ongoing neuronal membrane damage, neurodegeneration, and metabolic defects, consistent with a reduction in phosphatidylcholine species in postmortem brain tissue from dementia patients [7]. While some of the phosphatidylcholine species may be useful as biomarkers of disease activity, they likely will not translate into actionable items related to supplementation.

***Saliva*:** The acyl-alkyl phosphatidylcholines, PC ae C34:1-2, PC ae C36:1-2-3, PC ae C38:1c3, and PC ae C40:2-3 were found to be reduced in the saliva of AD patients (n=25) relative to controls (n=25) [8]. Levels of PC ae C36:1-2-3 were also decreased in the saliva of individuals with mild cognitive impairment (MCI) (n=25). No significant changes were seen between AD patients and controls for saliva levels of diacyl-phosphatidylcholines, lyso-acyl-phosphatidylcholines, and sphingomyelins.

***CSF*:** Phosphatidylcholines in the CSF are expected to be more representative of brain phosphatidylcholines relative to plasma levels, but have not shown clear utility as a cognition biomarker to date [6]. The association of 19 CSF phosphatidylcholine species with measures of cognition, neurodegeneration, and amyloid deposition was assessed in 655 cognitively unimpaired participants from the Mayo Clinic Study of Aging [6]. The total CSF phosphatidylcholine concentration nor individual CSF phosphatidylcholines were cross-sectionally or longitudinally associated with neuroimaging measures, cognitive measures, or the risk of MCI in multivariate analyses. CSF total phosphatidylcholine levels were cross-sectionally associated with worse global cognition, language, and attention z-scores and with lower hippocampal volume z-score, while higher levels of PC C36:3, PC C38:0, PC C38:5, PC C16:0_22:6 were associated with lower attention z-scores, and PC C36:5 was cross-sectionally associated with lower hippocampal volume, only in univariate analyses. A separate biomarker discovery

study found that CSF concentrations of dipalmitoyl-PC (PC 32a:0) were significantly associated with p-tau in their discovery (n=47) and validation cohorts (n=46) of individuals with normal cognition or MCI [9]. Total levels of saturated, but not mono- or polyunsaturated phosphatidylcholines in the CSF correlated with p-tau. The association may stem from a connection between dietary saturated fats and tau pathology, rather than phosphatidylcholine lipid species per se.

Plasma: A plasma lipidomics study comparing 148 AD patients with 152 elderly controls found significant overlap in the lipid signatures associated with AD and with brain atrophy in the hippocampus/entorhinal cortex [10]. The phospholipid PC 40:4 was strongly associated with AD, while elevated PC 36:3 was associated with a faster rate of decline, suggestive of altered acyl-chain remodeling of phospholipids in AD. A study developing predicative metabolic networks from 656 serum samples (ADNI cohort) found sex-specific signatures [11]. The male network was largely comprised of amino acids, while the female network was comprised of lipids, including phosphatidylcholines. The ApoE4 network was characterized by a signature of phosphatidylcholines mediated by PC aa C34:4. A plasma biomarker study assessing prognostic markers for progression including 48 participants found shifts in various phosphatidylcholine species when individuals converted to AD and in individuals with MCI that converted back to normal cognition during the 7-to-9-year follow-up period [12]. In a cross-sectional analysis including 205 AD patients and 207 controls, the phosphatidylcholine species PC36:5 and PC38:6 were found to be reduced in the plasma of AD patients [13]. Additionally, PC36:5 was also found to be associated with hippocampal volume, with lower levels observed in the context of atrophy. In a cohort of 1,440 cognitively unimpaired participants from the Mayo Clinic Study of Aging, higher levels of PC aa 14:0_14:0, PC aa 16:0_18:2, PC aa 18:0_18:1, and PC aa 18:1_18:1 were associated with better performance on tests of global cognition, memory, language, and attention in univariate cross-sectional analysis, but these associations were attenuated in multivariate analyses [14]. Longitudinally, higher levels of PC aa 16:0_18:2, PC aa 18:0_18:1 and PC aa 18:1_18:1 were also associated with slower decline on measures of global cognition. Higher levels of PC aa 14:0_14:0 were associated with slower amyloid deposition based on Aβ PET SUVR, and cortical thinning in longitudinal analysis, and with higher glucose metabolism in cross-sectional analysis. Alterations in serum phosphatidylcholine profiles were also a defining feature of patients with cognitive impairment coupled with hearing loss [15].

Human research to suggest benefits to patients with dementia:

A variety of RCTs have generally failed to successfully treat Alzheimer's or cognitive aging with lecithin, phosphatidylcholine supplements, or krill oil, although one or two trials reported some minimal effect. For example, a 2003 Cochrane meta-analysis reported on 10 trials in Alzheimer's patients, one trial in Parkinson's, and one trial in patients with subjective memory impairment. No benefits of any kind were reported in the Alzheimer's or Parkinson's patients; some benefits were reported in the one trial with subjective memory impairment but these effects have not been replicated [16].
The trials, although not promising, have all been short term, and longer-term trials could theoretically allow for more benefit.

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

There are several mechanistic rationales behind phosphatidylcholine/lecithin supplementation. Treatment can raise choline levels, providing a precursor for the synthesis of acetylcholine, a neurotransmitter lost early in Alzheimer's disease (AD), and also the target of most FDA-approved drugs for AD. Phosphatidylcholine is also a major component of cell membranes and critical for some types of intracellular signaling.

APOE4 interactions: Uncertain. Apolipoprotein E binds to phospholipids (eg. phosphatidylcholine) and this binding is slightly altered with ApoE4. However, this binding should not affect the primary suggested mechanisms of action of phosphatidylcholine, of providing a source of choline for acetylcholine synthesis and a source of phosphatidylcholine for cell membrane integrity. Thus far, observational studies have not indicated that the requirements for phosphatidylcholine differ based on ApoE4 status.

Aging and related health concerns: Higher circulating polyunsaturated phosphatidylcholines are associated with healthspan and lower mortality, which may reflect dietary choices. Adequate choline consumption may help protect against liver disease.

Types of evidence:

- 1 meta-analysis of studies assessing choline consumption and cancer risk
- 1 meta-analysis of RCTs testing delayed-release phosphatidylcholine for ulcerative colitis
- 4 observational studies with blood phosphatidylcholine levels and longevity/mortality
- 3 observational studies on dietary phosphatidylcholine and cardiometabolic disease/mortality
- 1 observational study on blood phosphatidylcholine levels and cardiovascular health

- 1 observational study on blood phosphatidylcholine levels and frailty
- 1 review of trials testing essential phospholipids in fatty liver disease
- 1 open-label trial testing essential phospholipids in NAFLD

Longevity: HIGHER LEVELS OF UNSATURATED PHOSPHATIDYLCHOLINES ASSOCIATED WITH REDUCED MORTALITY AND BETTER HEALTH OUTCOMES
Lipid classes associated with biological aging were assessed in 4,181 participants from the population-based Rhineland Study [17]. Higher levels of polyunsaturated phosphatidylcholines were associated with slower biological aging, which may be related to their antioxidant and cardioprotective properties. Phosphatidylcholine species with odd-numbered fatty acid tail lengths were associated with slower biological aging, while even-numbered fatty acid tail lengths were associated with faster biological aging in this cohort. These associations may stem from the impact of dietary choices on aging, as even-numbered saturated fatty acids are produced via the conversion of carbohydrates and alcohol to fatty acids. Phosphatidylcholine levels in the blood associated with mortality risk in a 2014 cohort publication but the direction of the association depended heavily on the type of lipid linked to phosphatidylcholine. Saturated and monounsaturated phosphatidylcholine were associated with a higher risk of mortality while long-chain polyunsaturated fatty acids (omega-3 or omega-6) were associated with less risk of mortality. Combining the six lipids with the most protective association and the six lipids with the most harmful association predicted a three-times increased risk of mortality. These effects might be related to diet and exercise [18].
In the Spanish Seniors-ENRICA 2 cohort, comprising 1,488 individuals ≥65 years old, higher plasma levels of total cholines (coefficient per one standard deviation [1-SD] increase: -1.48, 95% CI -1.99 to 0.96) and phosphatidylcholines (coefficient per 1-SD increase: -1.23, 95% CI -1.74 to -0.71) were associated with lower levels of multimorbidity, such that higher levels were associated with lower odds of cerebrovascular disease, chronic obstructive pulmonary disease, and peripheral vascular disease [19]. Additionally, higher levels of total cholines (Odds Ratio [OR]: 0.92, 95% CI 0.86 to 0.99) and phosphatidylcholines (OR: 0.93, 95% CI 0.87 to 0.99) were associated with lower odds of peripheral neuropathy. Phosphatidylcholines were among the characteristic metabolites associated with longevity in a study comparing centenarians with elderly adults (ages 60-70) (n=61) [20]. The phosphatidylcholine species 16:0/17:1 was upregulated in centenarians.

A study in *C. elegans* found that phosphatidylcholine supplementation increased survival under oxidative stress conditions, and extended mean survival in wild type worms by 17.8% and 22.2% at the 10 mg/l and 100 mg/l doses, respectively. Supplementation also delayed age-related motility

impairments and protected against Aβ-related toxicity. The increase in survival was coupled with a reduction in fertility.

Cardiovascular disease: MIXED ASSOCIATIONS IN OBSERVATIONAL STUDIES MAY BE RELATED TO DIETARY SOURCE OF PHOSHPHATIDYLCHOLINE

All-cause mortality and cardiovascular-related mortality were assessed in relation to dietary phosphatidylcholine intake in an observational study including 80,978 women from the Nurses' Health Study (1980–2012) and 39,434 men from the Health Professionals Follow-Up Study in the United States [21]. Following multivariable adjustment, higher phosphatidylcholine intake was associated with higher risk for all-cause mortality, with an HR of 1.11 (95% CI 1.06 to 1.17) for the highest quintile of intake, such that each 100-mg/d increase in phosphatidylcholine intake was associated with an 8% (95% CI 5% to 11%) increase in all-cause mortality. Similarly, each100-mg/d increase in phosphatidylcholine intake was associated with a 13% (95% CI 7% to 19%) increase in cardiovascular-related mortality, with an HR of 1.26 (95% CI 1.15 to 1.39) for the highest quartile of intake. The effects were primarily driven by diabetic participants. This group also found that each dietary increase in 100 mg choline from phosphatidylcholine increased the risk of type 2 diabetes by 17% (95% CI 13 to 22%) in the same study cohort [22]. In contrast, in the Kuopio Ischaemic Heart Disease Risk Factor Study in Finland including 2,332 men, individuals with higher choline (HR: 0.75, 95% CI 0.57 to 0.98) and phosphatidylcholine (HR: 0.59, 95%CI 0.45 to 0.78) intake had a lower risk of developing diabetes over a 19.3-year follow-up period [23].

The discrepancies across studies are thought to be related to differences in dietary patterns in terms of the predominant choline and phosphatidylcholine-rich foods consumed in different countries, as well as differences in the composition of gut microbiomes across populations [24]. Aside from eggs, fish appears to be a major source of choline and phosphatidylcholine intake in Nordic countries, such as Finland, whereas red meat makes up a larger proportion of dietary phosphatidylcholine intake in countries consuming a 'Western diet", such as the United States. The major driver of choline-related cardiovascular-related risk is thought to stem from the production of trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite of choline. The association of TMAO levels with mortality was assessed in 6,785 adults from the Multi-Ethnic Study of Atherosclerosis [25]. Higher TMAO levels were associated with higher risk for all-cause mortality (HR: 1.12, 95% CI 1.08 to 1.17), cardiovascular-related mortality (HR: 1.09, 95% CI 1.00 to 1.09), and kidney failure-related mortality (HR:1.44, 95% CI 1.25 to 1.66). Different forms of choline are preferentially metabolized to form TMAO. Several studies have found that phosphatidylcholine supplementation is not associated with elevated levels of TMAO [26; 27;

28; 29]. Similar findings have been shown with short term egg consumption [29]. This suggests that red meat consumption may be a major driver of the association between dietary phosphatidylcholine and cardiovascular disease in some populations, as red meat is high in both choline and carnitine, which are both precursors for TMAO [30]. Additionally, it has been shown that the production of TMAO is highly heterogenous across individuals depending on the composition of their gut microbiome [28]. Since the observational studies assessing dietary phosphatidylcholine did not also assess the levels of circulating TMAO in these individuals, it difficult to interpret the findings of these studies or assess their translatability to populations which may have different diets and microbiomes.

Although the exact species differ across studies, in general, circulating levels of polyunsaturated phosphatidylcholines appear to be associated with lower risk of mortality and better overall health. In a case-cohort sample of the PREDIMED trial (n=983), baseline plasma levels of polyunsaturated phosphatidylcholines showed inverse associations with cardiovascular disease, though there was no significant change in this lipid risk profile in response to the Mediterranean diet intervention in this study [31]. Although animal sources provide higher levels of cholines, the profile in plant sources may be more in line with positive health outcomes. Soybean-derived phosphatidylcholines are enriched in polyunsaturated species [32]. In a cross-sectional analysis including 735 participants from the Baltimore Longitudinal Study of Aging, higher levels of plant protein consumption were associated with particular beneficial phosphatidylcholine species, and with lower levels of frailty [33].
The relationship between choline and atherosclerotic disease has also been mixed in preclinical studies, which may be related to the use of different sources of choline. A recent study found that phosphatidylcholine supplementation, in the form of soy lecithin containing 23% phosphatidylcholine was protective against atherosclerosis in male Ldlr−/− mice [34].

Non-alcoholic fatty liver disease: POTENTIAL BENEFIT FOR HEPATOPROTECTION
Choline is essential for liver function, and choline deficiency is associated with the induction of fatty liver disease [32]. As such, the maintenance of adequate choline levels likely plays a greater role in the prevention of fatty liver disease than as a therapeutic option for established disease. Preparations of essential phospholipids, containing soybean-derived polyenylphosphatidylcholine have been tested in clinical studies for patients with liver disease [35]. Essential phospholipids are recommended in the treatment of non-alcoholic fatty liver disease (NAFLD) in Russia, China, Latvia, and Poland [35]. The essential phospholipid extracts contain standardized contents of 73%–79% to 92%–96% phosphatidylcholine, though most of the clinical studies used preparations containing 76% phosphatidylcholine.

In the 24-week prospective real-life observational MANPOWER study in Russia (NCT00063622), 2,843 adults newly diagnosed with NAFLD with at least one of four major comorbidities (obesity, hypertension, type 2 diabetes mellitus, or hypercholesterolemia) received 1.8 g/day of polyenylphosphatidylcholine in the form of essential phospholipids as an adjunct to the standard of care [36]. At the end of the study, there was a higher percentage of individuals with normalized liver enzyme levels, relative to the study initiation. Levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) were normal in 75.8%, 89.2%, and 62.5% of patients, respectively, compared to 36.2%, 52.3%, and 39.8% of patients with normal levels of the respective enzymes at baseline. The mean decrease in ALT levels ranged from 19.7 to 22.0 U/L, while the decrease in AST ranged from 16.9 to 18.4 U/L, and the decrease in GGT ranged from 17.2 to 18.7 U/L. Improvements in lipid parameters were seen both in groups taking the essential phospholipids alone and those taking them in conjunction with statins or fibrates. Improvements in liver echogenicity was observed in 63.8% of patients (95% CI 66.6% to 70.1%), while improvements in liver structure were seen in 42.7% of patients (95% CI 40.9% to 44.5%) [37]. Due to the lack of a control arm, the contribution of phosphatidylcholine to these effects is difficult to determine. A review of 20 trials testing essential phospholipids in patients with fatty liver disease indicated that essential phospholipids have also been shown to be beneficial as an add-on to diabetic medication, including metformin and insulin, or lifestyle interventions, to improve symptoms of diabetes-related fatty liver disease [35].

In a trial of healthy volunteers (n=30), treatment with lycosome formulated phosphatidylcholine (450 mg) facilitated clearance of acetaldehyde in the serum, prevented the reduction in total antioxidant capacity of serum, and mitigated the induction of oxidative stress markers (malonic dialdehyde) following alcohol consumption [38].

Protective mechanisms identified in preclinical studies include the mitigation of oxidative stress, apoptosis, lipoprotein oxidation and steatosis [32]. The abundant CYP enzyme, CYP2E1, which has been shown to be elevated in the context of fatty liver disease, and implicated in insulin resistance, is downregulated by polyenylphosphatidylcholine. Polyenylphosphatidylcholine has also been shown to exert anti-inflammatory effects through the metabolic reprogramming of Kupffer macrophages from pro-inflammatory M1-like towards anti-inflammatory M2-like. Polyenylphosphatidylcholine may also help restore membrane function and structure by acting as a source to replenish the membrane localized phosphatidylcholine.

Ulcerative colitis: POTENTIAL BENEFIT FOR DELAYED-RELEASE FORMULATIONS

Phosphatidylcholine plays an important role in the intestinal lining as a hydrophobic barrier against bacteria [39]. Colonic phosphatidylcholine is derived from the secretion of systemic phosphatidylcholine

into the ileum. It translocates across the membrane due to charge differentials, and this translocation process is disrupted in the context of colitis, leading to a reduction in levels of colonic mucosal phosphatidylcholine, and increasing the risk for inflammation inducing bacterial invasion. Conventional oral preparations of phosphatidylcholine are absorbed and not available for the colonic mucosa necessitating the use of encapsulated delayed release formulations. Delayed release phosphatidylcholine preparations have been tested in clinical trials for ulcerative colitis. A meta-analysis of three RCTs including 160 patients found that delayed-release phosphatidylcholine was associated with an improved rate of clinical remission (OR: 9.68, 95% CI 3.81 to 24.6), clinical activity (OR: 30.58 , 95% CI 8.01 to 116.82), endoscopic outcomes (OR: 36.73 , 95% CI 8.39 to 160.8), histology (OR: 3.99, 95% CI 1.36 to 11.67), and quality of life (OR: 7.59, 95% CI 3.33 to 17.31) [39]. Benefits were seen with preparations containing delayed intestinal release 30% phosphatidylcholine enriched lecithin at doses ≥ 1 g, whereas highly enriched (94%) gastric acid preparations were not effective, possibly due to microbial metabolism and reduced stability.

Osteoarthritis: PHOSPHATIDYLCHOLINES MAY BE A BIOMARKER
The ratio of serum phosphatidylcholines (PCs) to lysoPCs was identified as a biomarker of osteoarthritis disease progression in terms of joint degradation and cartilage loss [40]. The associations likely stem from the overactivation of the conversion of PCs into lysoPCs catalyzed by PLA2. LysoPC, also called lysolecithin, promotes phagocyte recruitment and chondrocyte apoptosis, leading to cartilage damage. Additionally, elevated PLA2 activity results in the production of inflammatory mediators, such as the long-chain fatty acid arachidonic acid. The expression of PLA2G5, was found to be increased by 85% in cartilage and by 19% in synovial membranes from individuals with osteoarthritis, which was correlated with elevations of the inflammatory cytokines, IL-6 and TNF-α. This ratio was also found to be a marker of treatment response in 158 participants from a 24-month clinical trial comparing licofelone with naproxen [41]. Responders had higher lysoPC to PC ratios relative to non-responders, such that there was an approximately three times greater probability of response with cutoff ratio of 0.088.

Cancer: POTENTIAL BENEFIT/UNCLEAR
Metabolic reprogramming is a prominent feature of cancer cells. Elevations in phosphatidylcholine are part of a cholinergic phenotype as well as a characteristic of highly proliferative cells [42]. These metabolic changes involving phosphatidylcholine may contribute to cancer cell survival and drug resistance. However, most observational studies are biased in the direction of choline and lecithin supplementation showing associations with reduced cancer risk (pooled Relative Risk 0.8, 95% CI 0.70 to

0.97) [43], suggesting that these metabolic changes stem from malignant transformation rather than choline intake.
Prostate cancer: High dietary intake of choline (primarily lecithin) associated with a 70% higher risk of lethal prostate cancer (HR: 1.7, 95% CI 1.18 to 2.45) although this association could be due to other components of typical dietary sources of choline (meat, milk, and eggs) [44].
Hepatocellular carcinoma (HCC): A biomarker study including 400 patient tissues samples identified a reprogramming of lipid metabolism in the context of HCC [45]. Phosphatidylcholines were significantly downregulated as part of this reprograming. The species PC O-16:0/20:3(8Z, 11Z, 14Z), and PC (16:1(9Z)/P-18:0) showed utility in diagnostic metabolite panels for HCC.

Safety: Phosphatidylcholine is widely consumed as part of a normal diet, and aside from mild gastrointestinal events, supplementation is generally well-tolerated. Unlike some other forms of choline, it is not associated with elevations in TMAO.

Types of evidence:

- 1 meta-analysis of RCTs testing delayed-release phosphatidylcholine for ulcerative colitis trials
- 1 review of essential phospholipids for fatty liver disease
- 5 clinical trials assessing TMAO production following phosphatidylcholine consumption
- 5 observational studies assessing role of phosphatidylcholine intake on disease risk

Phosphatidylcholine derived from lecithin has been granted generally recognized as safe (GRAS) status. Oral phosphatidylcholine has generally not been associated with serious adverse events, though some minor events have been reported including excessive sweating and gastrointestinal events (Drugs.com). Essential phospholipids are widely used in several countries as a hepatoprotective agent, and generally considered safe [35]. Safety data in clinical studies using essential phospholipids is poorly reported, but the most commonly reported adverse events are mild gastrointestinal events.

The primary concern with choline supplementation in general has been elevations in the pro-inflammatory gut-derived metabolite TMAO. Although there have been some observational studies suggesting links between increased dietary phosphatidylcholine intake with increased mortality risks with an assumption that TMAO was a mediator [21], these studies did not conclusively show that phosphatidylcholine intake specifically drove TMAO levels in these individuals. Moreover, there have

been numerous clinical studies showing that other forms of choline supplements, such as choline bitartrate, induce TMAO production, while phosphatidylcholine supplementation does not lead to elevations in blood levels of TMAO [26; 27; 28; 29]. Similarly, some studies have found that consumption of phosphatidylcholine-rich eggs also do not promote the production of TMAO [29].

Drug interactions: Phosphatidylcholine is not known to interact with other medications.

Sources and dosing:

Choline is an essential nutrient. The adequate intake level recommendation by the European Food Safety Authority (EFSA) is 400 mg/day for adults, whereas that recommended level by the US Institute of Medicine is 550 mg/day for adults [4].
According to the USDA, foods that are highest in phosphatidylcholine include whole eggs (250 mg/100 g food), liver (200-250 mg/100 g food), pork (70-100 mg/100 g food), beef (50-90 mg/100 g food), shrimp (~70 mg/100 g food), soy (65 mg/100g food), pine nuts (45 mg/100 g food), almonds (40 mg/100 g food), flaxseed (36 mg/100 g food), and sunflower seeds (29 mg/100 g food) [46].

- **Phosphatidylcholine supplements.** Supplements can vary in their lipid content. Based on the mortality association study [18], supplements high in polyunsaturated fatty acids (either omega-3 or omega-6) might be beneficial while supplements high in saturated or monounsaturated lipids might be harmful. However, the ratios of these different lipids may be altered substantially by metabolism and exercise as well as dietary intake. Supplements taken orally in clinical trials range in dose from 350 mg to 6 g per day. For ulcerative colitis, delayed intestinal release 30% phosphatidylcholine enriched lecithin encapsulated with Eudragit S 100 at doses between 1 to 4 g per day was associated with benefits in small clinical trials.
- **Essential Phospholipids:** The dose used in the observational MANPOWER study suggestive of hepatoprotective effects was 1.8 g/day divided into three doses.
- **Lecithin:** Doses in randomized trials have ranged from 1 to 50 grams daily, generally with no major side effects reported. Lecithin is the major dietary source of phosphatidylcholine. It is a yellow-brown fatty substance found in egg yolk, organ meats, nuts, and spinach.

Research underway:

According to Clinicaltrials.gov, there are currently clinical trials testing supplemental phosphatidylcholine in NAFLD (NCT05200156), oral sunflower lecithin dietary supplementation on meibomian gland function in adults with dry eye disease (NCT06058559), phosphatidylcholine supplementation in pregnancy on attention and social withdrawal (NCT03028857), and a study examining the role gut flora plays in modulating metabolism of dietary carnitine and phosphatidylcholine in humans (NCT01731236).

Search terms:

Pubmed, Google: Phosphatidylcholine

- Alzheimer's disease, neurodegeneration, clinical trial, longevity, cardiovascular, cancer, clinical trial, safety

Websites visited for Phosphatidylcholine:

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

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