**Letters & Reviews in Neurological Sciences**

# Oils and Fats (Lipids) of Plant and Animal Origin in Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Risk, Prognosis, Dietary Therapy and Mechanisms

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ARTICLE INFO

Prepared 2nd October 2026,
www.esrapublications.com

Edited & Published 08th October 2026

ABSTRACT

Lipids occupy a unique position in amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND): energy balance is disturbed, weight loss predicts poor survival, and dietary fats have been proposed both as risk modifiers and as therapy. This review examines plant oils (rich in α-linolenic acid), marine oils, animal fats and cholesterol, and high-fat or ketogenic diets. In a pooled analysis of five cohorts (1,002,082 participants), higher intake of α-linolenic acid was associated with lower ALS risk (RR 0.73, 95% CI 0.59–0.89), marine ω-3 fatty acids showed a weaker association (RR 0.84, 95% CI 0.65–1.08), and ω-6 intake showed none [1]. Higher blood lipids have been linked to longer survival in some studies [2,3], but this link weakened after adjustment for body mass index [4], whereas genetic analysis suggests that elevated LDL cholesterol is a causal risk factor [5]. A high-energy diet extended survival by 20% in SOD1 mice [6], and a ketogenic diet delayed motor decline in the same model [7]. In humans, a small phase 2 trial showed that hypercaloric tube feeding is safe [8], and the LIPCAL-ALS trial found no overall survival benefit from a high-caloric fatty diet but a post hoc benefit in fast-progressing patients [9]. No oil or fat has been proven to slow ALS. Mechanisms, tables and graphs are provided, and research priorities are outlined.

*Key words*: Amyotrophic lateral sclerosis; motor neuron disease; dietary fat; omega-3 fatty acids; α-linolenic acid; cholesterol; ketogenic diet; high-calorie diet; energy metabolism.

## 1. Introduction and scope

ALS is characterised by progressive loss of upper and lower motor neurons, leading to paralysis and usually death from respiratory failure within a few years of onset [10,11]. Nutrition is a central clinical concern because weight loss is an independent prognostic factor [9].

This review covers lipids in the dietary and nutritional sense. Plant sources include vegetable oils and nuts, which supply α-linolenic acid (ALA) [1]; marine sources supply the long-chain ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid; and animal sources supply saturated fat and cholesterol. High-fat and ketogenic regimens are considered as nutritional strategies. An important limitation is stated at the outset: No randomised trial of a specific plant oil or animal fat as ALS treatment was identified, so evidence comes from observational and genetic studies, animal models,

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and trials of high-calorie diets. The relation between lipid sources and ALS mechanisms is summarised in Figure 1.

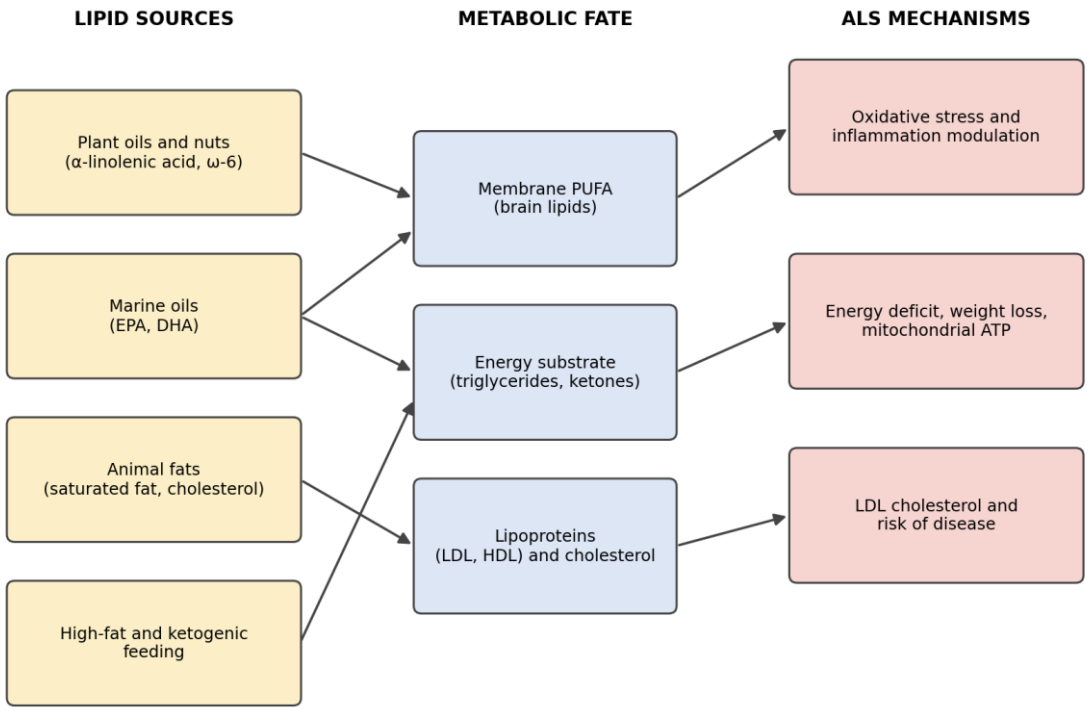



*Figure 1. Lipid sources, their metabolic fates and the ALS mechanisms they may influence.*

## 2. Lipid metabolism and energy balance in ALS

ALS is accompanied by a disturbance of energy homeostasis. In transgenic SOD1 mice, a metabolic deficit with reduced adipose tissue accumulation, increased energy expenditure and skeletal muscle hypermetabolism appears early, before symptoms; compensating this imbalance with a high-energy diet extended mean survival by 20% [6]. In patients, weight loss is an independent prognostic factor [9], and a lipid-rich diet has been proposed for patients who lose weight, although this requires proof from controlled trials [3]. These observations make lipids relevant primarily as an energy source, in addition to any specific biological effect of individual fatty acids.

## 3. Plant oils and ω-3 fatty acids

### *3.1 α-Linolenic acid and marine ω-3 fatty acids*

Diet-derived long-chain polyunsaturated fatty acids (PUFAs) are incorporated in brain lipids and modulate oxidative and inflammatory processes [1]. In five prospective cohorts with 1,002,082 participants, higher intake of total ω-3 PUFA was associated with reduced ALS risk, an effect contributed by both ALA (RR 0.73, 95% CI 0.59–0.89, highest versus lowest quintile) and marine ω-3 PUFA (RR 0.84, 95% CI 0.65–1.08), whereas ω-6 intake was not associated with risk [1] (Figure 3a). A Dutch case-control study had earlier reported that higher intake of polyunsaturated fatty acids together with vitamin E was associated with lower risk [12].

### *3.2 A caution from animal models*

The animal evidence for marine ω-3 fatty acids is not supportive. Dietary EPA was reported to accelerate disease progression in an ALS mouse model [13], which is the opposite of what the cohort data would predict. The authors of the cohort study found that plant-derived ALA appeared stronger

than marine ω-3 [1]. The associations may therefore reflect the broader diet, the specific fatty acid, or confounding, and no trial has tested ω-3 supplementation in ALS patients.

## 4. Animal fats, cholesterol and blood lipids

Several clinical studies found that higher serum lipids accompany longer survival. Dyslipidemia was described as a protective factor in ALS [2]. In 488 patients, high fasting cholesterol and triglycerides were associated with significantly better survival, and a triglyceride level above the median was associated with a median 14 months' longer life expectancy [3]. However, in 427 patients from three clinical trial databases, dyslipidemia was not an independent predictor of survival, and body mass index (BMI) was [4]. The lipid-survival association therefore seems to reflect nutritional reserve rather than a direct effect of cholesterol.

The picture for risk differs. A Mendelian randomization analysis found evidence that hyperlipidemia is a causal risk factor for ALS and that elevated LDL cholesterol is a causal risk factor [5]. Taken together, the findings suggest a paradox: genetically higher LDL cholesterol may raise the risk of developing ALS, whereas in established disease higher lipid levels mark better nutritional status and longer survival. Practical conclusions follow cautiously: Lipid-lowering treatment in established ALS should be considered individually, as the authors of the 488-patient study advised [3].

**Table 1.** Observational and genetic studies of lipids and ALS.

| Study | Design | Main finding (as reported) |
|---|---|---|
| Fitzgerald et al. [1] | Pooled analysis of 5 cohorts; 1,002,082 participants | ALA RR 0.73 (0.59–0.89); marine ω-3 RR 0.84 (0.65–1.08); ω-6 not associated. |
| Veldink et al. [12] | Case-control; Netherlands | Higher PUFA and vitamin E intake associated with lower risk. |
| Dupuis et al. [2] | Patient study of blood lipids | Dyslipidemia described as a protective factor. |
| Dorst et al. [3] | 488 patients; fasting lipids | High cholesterol and triglycerides: longer survival; median +14 months above median triglycerides. |
| Paganoni et al. [4] | 427 patients; 3 trial databases | BMI, not dyslipidemia, independently predicts survival. |
| Bandres-Ciga et al. [5] | Mendelian randomization; >700 traits | Hyperlipidemia and elevated LDL cholesterol: causal risk factors. |

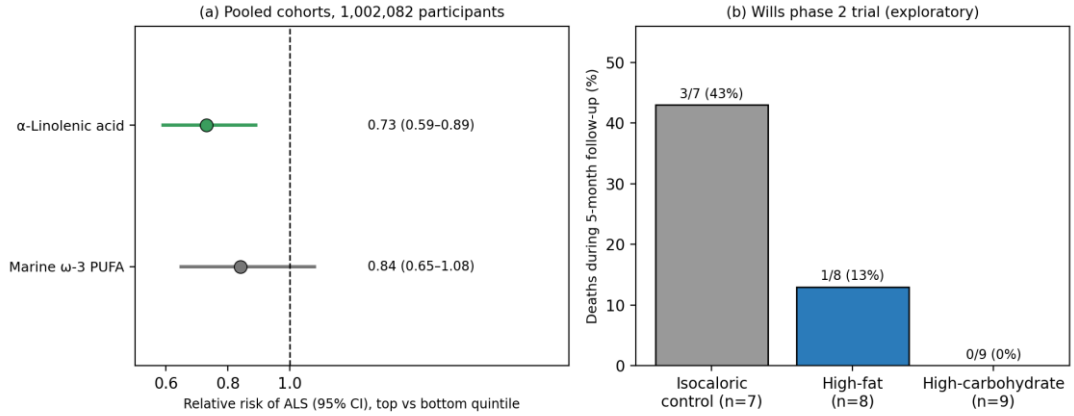



*Figure 3. Reported values from Fitzgerald et al. 2014 (a) and Wills et al. 2014 (b); plotted from values in each source. Panel (b) numbers are tiny and exploratory.*

## 5. High-fat, high-calorie and ketogenic diets

### *5.1 Preclinical evidence*

A high-energy diet extended survival by 20% in SOD1 mice [6]. A ketogenic diet, tested in SOD1-G93A mice, delayed the loss of 50% of baseline motor performance by 25 days, kept animals heavier and protected motor neurons, although the age at death was not significantly different from that of mice on a standard diet; the ketone body D-β-hydroxybutyrate improved mitochondrial ATP production [7]. The ketogenic diet therefore shows functional and neuroprotective effects in mice, but no clear survival gain.

### *5.2 Clinical evidence*

In a randomised, double-blind phase 2 trial, 24 patients with advanced ALS already on tube feeding received an isocaloric control diet, a high-carbohydrate hypercaloric diet or a high-fat hypercaloric diet; the study concluded that hypercaloric enteral nutrition is safe and tolerable and supported larger trials at earlier stages [8]. During follow-up, 3 of 7 control patients died, compared with 1 of 8 in the high-fat group and none of 9 in the high-carbohydrate group, but these exploratory numbers are far too small for conclusions [8]. In the LIPCAL-ALS trial of 201 patients, a high-caloric fatty diet did not prolong survival in the whole population (survival probability 0.37 versus 0.39 at 28 months; hazard ratio 0.97), but post hoc analysis showed a significant survival benefit in fast-progressing patients [9] (Figure 4a). No clinical trial of a ketogenic diet in ALS was identified in the sources used here.

**Table 2.** Preclinical and interventional studies of lipid-based nutrition in ALS.

| Study | Intervention | Design | Outcome (as reported) |
|---|---|---|---|
| Dupuis et al. [6] | High-energy diet | SOD1 mice | Mean survival extended by 20%. |
| Zhao et al. [7] | Ketogenic diet | SOD1-G93A mice | Motor decline delayed by 25 days; neurons protected; survival not significantly different. |
| Yip et al. [13] | Dietary EPA | ALS mouse model | Accelerated disease progression. |
| Wills et al. [8] | Hypercaloric tube feeding (high-fat or high-carbohydrate) | Randomised phase 2; 24 patients | Safe and tolerable; exploratory survival signal. |
| Ludolph et al. [9] | High-caloric fatty diet | Randomised; 201 patients | No overall survival gain (HR 0.97); post hoc benefit in fast progressors. |

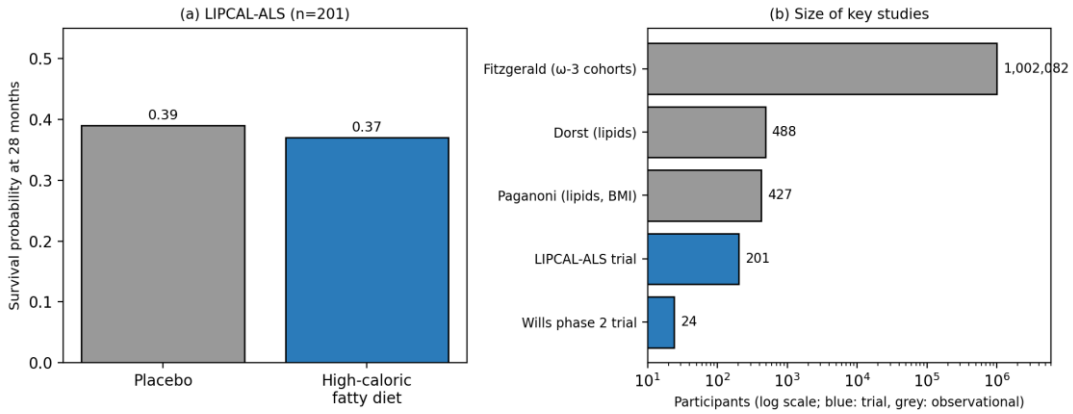



*Figure 4. Reported values from Ludolph et al. 2020 (a) and sample sizes of selected studies (b).*

## 6. Mechanisms of action

Proposed mechanisms fall into three groups (Figure 2). The first is membrane and inflammatory modulation: PUFAs incorporated in brain lipids modulate oxidative and inflammatory processes [1], which provides the rationale for plant and marine ω-3 oils. The second is energy supply: a metabolic deficit with hyper-metabolism is present in transgenic mice and can be offset by a high-energy diet [6], and ketones promote mitochondrial ATP production and may stabilise membranes [7]. The third is cholesterol and lipoprotein biology: LDL cholesterol appears causal for disease risk [5], whereas blood lipid levels in established disease mainly reflect nutritional reserve [4]. These mechanisms are partly preclinical and may act through different routes, which may explain why risk and survival associations point in different directions.

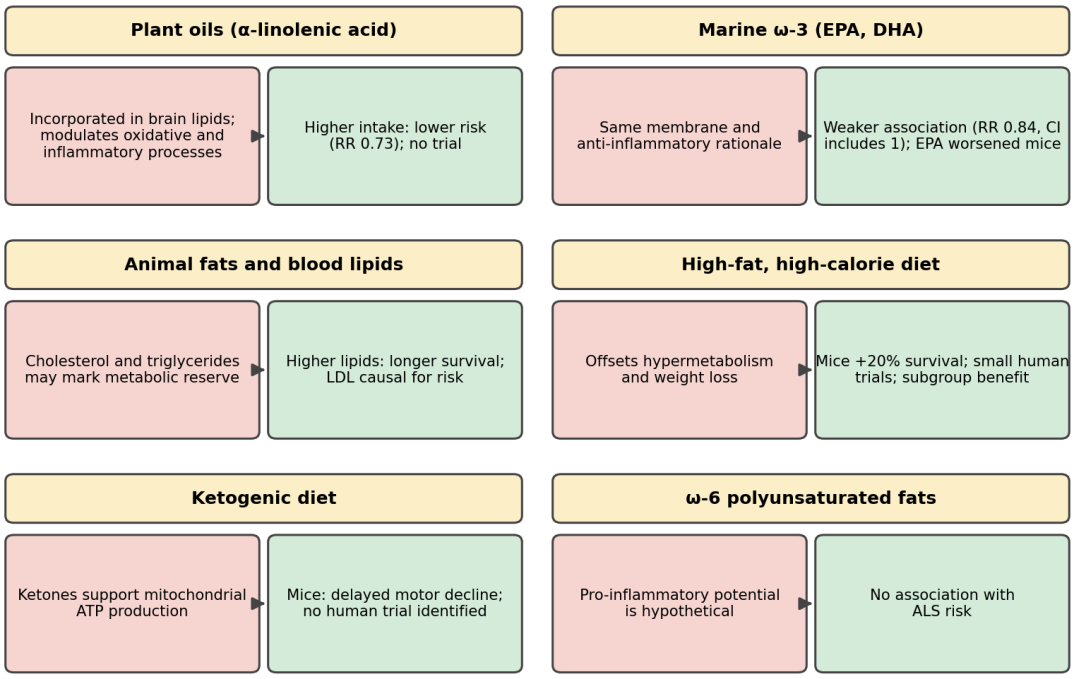



*Figure 2. Proposed mechanisms (left) and evidence status (right) for the main lipid groups.*

## 7. Comparative assessment of lipid sources

Table 3 compares the lipid groups. Plant-derived ALA has the most consistent protective signal, but only in observational data [1]. Marine ω-3 is weaker and potentially harmful in mice [1,13]. Animal fats and cholesterol present an unresolved paradox between risk and survival [3–5]. High-fat feeding is promising for weight maintenance but has not shown overall survival benefit [9]. Figure 5 summarises the type of evidence for each.

**Table 3.** Lipid groups considered for ALS/MND: evidence and assessment.

| Lipid group | Evidence | Evidence type | Assessment |
|---|---|---|---|
| Plant oils (ALA) | Lower risk with higher intake [1] | Observational | Supports ALA-rich diet; unproven as therapy |
| Marine ω-3 (EPA, DHA) | Weaker association [1]; EPA worsened mice [13] | Observational; mouse | Mixed; no supplementation trial |
| ω-6 PUFA | No association with risk [1] | Observational | No signal |
| Animal fats, cholesterol | LDL causal for risk [5]; lipids linked to survival [3] | Genetic; observational | Paradox; individualise |
| High-fat, high-calorie diet | Mice +20% survival [6]; fast-progress or benefit [9] | Mouse; randomised trials | Weight maintenance; needs confirmation |
| Ketogenic diet | Delayed motor decline in mice [7] | Mouse | Preclinical only |




*Figure 5. Qualitative evidence map for lipids in ALS/MND; cells reflect reported direction, not effect size.*

## 8. Limitations and future directions

Key limitations are the absence of trials of specific oils or fats, retrospective dietary assessment, residual confounding by weight and nutritional status [4], small phase 2 trials [8], and reliance on mouse models whose findings do not always agree with human data [1,13]. Priorities include: (i). randomised trials of ALA-rich oils with biomarker and functional endpoints; (ii). prospective confirmation of the benefit of high-caloric fatty nutrition in fast-progressing patients [9]; (iii). human studies of ketogenic regimens building on mouse findings [7]; (iv). clarification of the risk–survival paradox for LDL cholesterol using genetic and longitudinal data [4,5] and (v). attention to safety, since ketogenic and high-fat regimens may affect cholesterol. Patients should receive individual nutritional assessment before any change in diet.

## 9. Conclusions

No oil or fat of plant or animal origin has been shown to slow ALS. Observational data favour plant-derived α-linolenic acid [1], high-fat feeding is useful mainly to maintain weight and may help fast-progressing patients [9], and cholesterol shows a paradoxical relation with risk and survival [3–5]. Nutrition in ALS should aim to prevent weight loss under professional supervision, and lipid-based interventions should be tested in carefully designed trials before being recommended as disease-modifying therapy.

## Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological disorders.

Funding: No specific funding was received for preparation of this review.
Conflict of interest: The author declares no conflict of interest.
Ethics approval: Not applicable; this article is a literature-based narrative review and contains no new human or animal data.
Data availability: No new datasets were generated or analyzed.

## Author Note

This manuscript is a literature review and is not a treatment recommendation for any individual patient. Oils and Fats (Lipids) supplementation should be undertaken only for a clinically justified indication and with appropriate medical monitoring under the supervision of an expert neurologist.

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